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

Cancer Pharmacogenomics.

Agosto - Septiembre 2013 / August - September 2013

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[1]

TÍTULO / TITLE: - Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Sep 12;369(11):1023-34. doi: 10.1056/NEJMoa1305275.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1305275](#)

AUTORES / AUTHORS: - Douillard JY; Oliner KS; Siena S; Tabernero J; Burkes R; Barugel M; Humblet Y; Bodoky G; Cunningham D; Jassem J; Rivera F; Kocakova I; Ruff P; Blasinska-Morawiec M; Smakal M; Canon JL; Rother M; Williams R; Rong A; Wizezorek J; Sidhu R; Patterson SD

INSTITUCIÓN / INSTITUTION: - Institut de Cancerologie de l'Ouest (ICO) Rene Gauducheau, Nantes, France. jean-yves.douillard@ico.unicancer.fr

RESUMEN / SUMMARY: - BACKGROUND: Patients with metastatic colorectal cancer that harbors KRAS mutations in exon 2 do not benefit from anti-epidermal growth factor receptor (EGFR) therapy. Other activating RAS mutations may also be negative predictive biomarkers for anti-EGFR therapy. METHODS: In this prospective-retrospective analysis, we assessed the efficacy and safety of panitumumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) as compared with FOLFOX4 alone, according to RAS (KRAS or NRAS) or BRAF mutation status. A total of 639 patients who had metastatic colorectal cancer without KRAS mutations in exon 2 had results for at

least one of the following: KRAS exon 3 or 4; NRAS exon 2, 3, or 4; or BRAF exon 15. The overall rate of ascertainment of RAS status was 90%. RESULTS: Among 512 patients without RAS mutations, progression-free survival was 10.1 months with panitumumab-FOLFOX4 versus 7.9 months with FOLFOX4 alone (hazard ratio for progression or death with combination therapy, 0.72; 95% confidence interval [CI], 0.58 to 0.90; P=0.004). Overall survival was 26.0 months in the panitumumab-FOLFOX4 group versus 20.2 months in the FOLFOX4-alone group (hazard ratio for death, 0.78; 95% CI, 0.62 to 0.99; P=0.04). A total of 108 patients (17%) with nonmutated KRAS exon 2 had other RAS mutations. These mutations were associated with inferior progression-free survival and overall survival with panitumumab-FOLFOX4 treatment, which was consistent with the findings in patients with KRAS mutations in exon 2. BRAF mutations were a negative prognostic factor. No new safety signals were identified. CONCLUSIONS: Additional RAS mutations predicted a lack of response in patients who received panitumumab-FOLFOX4. In patients who had metastatic colorectal cancer without RAS mutations, improvements in overall survival were observed with panitumumab-FOLFOX4 therapy. (Funded by Amgen and others; PRIME ClinicalTrials.gov number, NCT00364013.).

[2]

TÍTULO / TITLE: - Prognostic Impact of Deficient DNA Mismatch Repair in Patients With Stage III Colon Cancer From a Randomized Trial of FOLFOX-Based Adjuvant Chemotherapy.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 9.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2013.48.9591](#)

AUTORES / AUTHORS: - Sinicrope FA; Mahoney MR; Smyrk TC; Thibodeau SN; Warren RS; Bertagnolli MM; Nelson GD; Goldberg RM; Sargent DJ; Alberts SR

INSTITUCIÓN / INSTITUTION: - Frank A. Sinicrope, Michelle R. Mahoney, Thomas C. Smyrk, Stephen N. Thibodeau, Garth D. Nelson, Daniel J. Sargent, and Steven R. Alberts, Mayo Clinic, Mayo Cancer Center and the North Central Cancer Treatment Group, Rochester, MN; Robert S. Warren, University of California San Francisco, San Francisco, CA; Monica M. Bertagnolli, Brigham and Women's Hospital, Boston, MA; and Richard M. Goldberg, The Ohio State University Comprehensive Cancer Center, Columbus, OH.

RESUMEN / SUMMARY: - PURPOSE: The association of deficient DNA mismatch repair (dMMR) with prognosis in patients with colon cancer treated with adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) chemotherapy remains unknown. PATIENTS AND METHODS: Resected, stage III colon carcinomas from patients (N = 2,686) randomly assigned to FOLFOX +/- cetuximab (North Central Cancer Treatment Group N0147 trial) were analyzed for mismatch repair (MMR) protein expression and mutations in BRAFV600E (exon 15) and KRAS (codons 12 and 13). Association of

biomarkers with disease-free survival (DFS) was determined using Cox models. A validation cohort (Cancer and Leukemia Group B 88903 trial) was used. RESULTS: dMMR was detected in 314 (12%) of 2,580 tumors, of which 49.3% and 10.6% had BRAFV600E or KRAS mutations, respectively. MMR status was not prognostic overall (adjusted hazard ratio [HR], 0.82; 95% CI, 0.64 to 1.07; P = .14), yet significant interactions were found between MMR and primary tumor site (Pinteraction = .009) and lymph node category (N1 v N2; Pinteraction = .014). Favorable DFS was observed for dMMR versus proficient MMR proximal tumors (HR, 0.71; 95% CI, 0.53 to 0.94; P = .018) but not dMMR distal tumors (HR, 1.71; 95% CI, 0.99 to 2.95; P = .056), adjusting for mutations and covariates. Any survival benefit of dMMR was lost in N2 tumors. Mutations in BRAFV600E (HR, 1.37; 95% CI, 1.08 to 1.70; P = .009) or KRAS (HR, 1.44; 95% CI, 1.21 to 1.70; P < .001) were independently associated with worse DFS. The observed MMR by tumor site interaction was validated in an independent cohort of stage III colon cancers (Pinteraction = .037). CONCLUSION: The prognostic impact of MMR depended on tumor site, and this interaction was validated in an independent cohort. Among dMMR cancers, proximal tumors had favorable outcome, whereas distal or N2 tumors had poor outcome. BRAF or KRAS mutations were independently associated with adverse outcome.

[3]

TÍTULO / TITLE: - Molecular detection of lymph node metastasis in breast cancer patients treated with preoperative systemic chemotherapy: a prospective multicentre trial using the one-step nucleic acid amplification assay.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17;109(6):1693-8. doi: 10.1038/bjc.2013.503. Epub 2013 Sep 3.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.503](#)

AUTORES / AUTHORS: - Osako T; Tsuda H; Horii R; Iwase T; Yamauchi H; Yagata H; Tsugawa K; Suzuki K; Kinoshita T; Akiyama F; Nakamura S

INSTITUCIÓN / INSTITUTION: - [1] Division of Pathology, The Cancer Institute of Japanese Foundation for Cancer Research, Tokyo, Japan [2] Department of Pathology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan.

RESUMEN / SUMMARY: - Background:For patients with breast cancer treated with preoperative chemotherapy, residual tumour burden in lymph nodes is the strongest prognostic factor. However, conventional pathological examination has limitations that hinder the accurate and reproducible measurement. The one-step nucleic acid amplification (OSNA) assay is a novel molecular method for detecting nodal metastasis. In this prospective multicentre trial, we assessed the performance of the OSNA assay in detecting nodal metastasis after chemotherapy.Methods:In total, 302 lymph nodes from 80 breast cancer patients who underwent axillary dissection after chemotherapy

were analysed. Each node was cut into two or four slices. One piece or alternate pieces were evaluated by pathology, and the other(s) were examined using the OSNA assay. The results of the two methods were compared. Stromal fibrosis, histiocytic aggregates, and degenerated cancer cells were regarded as chemotherapy-induced histological changes. Results: The overall accuracy, sensitivity, and specificity of the OSNA assay compared with the reference pathology were 91.1%, 88.3%, and 91.7%, respectively. Of the 302 lymph nodes, 66 (21.9%) exhibited chemotherapy-induced histology. For these nodes, the accuracy, sensitivity, and specificity were 90.9%, 88.9%, and 93.3%, respectively. Conclusion: The OSNA assay can detect the residual tumour burden as accurately as conventional pathology, although chemotherapy-induced histological changes are present.

[4]

TÍTULO / TITLE: - Prognostic impact of day 15 blast clearance in risk-adapted remission induction chemotherapy for younger patients with acute myeloid leukemia: long term results of the multicenter prospective LAM-2001 trial by the GOELAMS study group.

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

REVISTA / JOURNAL: - Haematologica. 2013 Aug 23.

●● [Enlace al texto completo \(gratis o de pago\) 3324/haematol.2013.091819](#)

AUTORES / AUTHORS: - Bertoli S; Bories P; Bene MC; Daliphard S; Lioure B; Pigneux A; Vey N; Delaunay J; Leymarie V; Luquet I; Blanchet O; Cornillet-Lefebvre P; Hunault M; Bouscary D; Fegueux N; Guardiola P; Dreyfus F; Harousseau JL; Cahn JY; Ifrah N; Recher C

INSTITUCIÓN / INSTITUTION: - Hopitaux Universitaires de Strasbourg, France;

RESUMEN / SUMMARY: - Early response to chemotherapy has a major prognostic impact in acute myeloid leukemia patients treated with a double induction strategy. Less is known about patients treated with standard-dose cytarabine and anthracycline. We designed a risk-adapted remission induction regimen in which a second course of intermediate-dose cytarabine was delivered after standard 7+3 only if patients had 5% or more bone marrow blasts fifteen days after chemotherapy initiation (d15-blasts). Of 823 included patients, 795 (96.6%) were evaluable. Five hundred and forty five patients (68.6%) had less than 5% d15-blasts. Predictive factors for high d15-blasts were white blood cell count ($p < 0.0001$) and cytogenetic risk ($p < 0.0001$). Patients with fewer than 5% d15-blasts had a higher complete response rate (91.7% vs 69.2%, $p < 0.0001$) and a lower induction death rate (1.8% vs 6.8%, $p = 0.001$). Five-year event-free (48.4% vs 25%, $p < 0.0001$), relapse-free (52.7% vs 36.9%, $p = 0.0016$) and overall survival (55.3% vs 36.5%, $p < 0.0001$) were significantly higher in patients with d15-blasts lower than 5%. Multivariate analyses identified d15-blasts and cytogenetic risk as independent prognostic factors for the three endpoints. Failure to achieve early blast clearance remains a poor prognostic factor even after early salvage. By contrast,

early responding patients have a favorable outcome without any additional induction course. NCT01015196.

[5]

TÍTULO / TITLE: - Pharmacogenetically driven patient selection for a first-in-human phase I trial of batracylin in patients with advanced solid tumors and lymphomas.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Oct;72(4):917-23. doi: 10.1007/s00280-013-2244-4. Epub 2013 Aug 3.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00280-013-2244-4](#)

AUTORES / AUTHORS: - Kummar S; Gutierrez ME; Anderson LW; Klecker RW Jr; Chen A; Murgo AJ; Doroshow JH; Collins JM

INSTITUCIÓN / INSTITUTION: - Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA.

RESUMEN / SUMMARY: - **PURPOSE:** Batracylin (daniquidone), an ATP-insensitive topoisomerase I/II inhibitor, demonstrated wide interspecies variation in preclinical models consistent with formation of a toxic metabolite, N-acetyl-batracylin, following metabolism by N-acetyl-transferase 2 (NAT2). To minimize exposure to this toxic metabolite, this first-in-human study was conducted in patients with advanced refractory solid tumors or lymphomas demonstrated to have a slow NAT2 acetylator genotype. The objectives were to determine the safety, maximum tolerated dose (MTD), and pharmacokinetics of batracylin and its metabolites. **METHODS:** Based on the MTD for rats, the most sensitive species, the starting dose was 5 mg/day for 7 days in 28-day cycles. Dose escalation followed accelerated titration design 4B, with restaging performed every 2 cycles. **RESULTS:** Thirty-one patients were enrolled. Treatment was well tolerated; one patient experienced grade 3 toxicity (lymphopenia). Dose escalation was stopped at 400 mg/day due to grade 1 and 2 hemorrhagic cystitis. No objective responses were observed, but prolonged disease stabilization was observed in 2 patients, one with peritoneal mesothelioma (8 cycles) and another with adrenocortical cancer (18 cycles). Across an 80-fold range of doses, the ratios of systemic exposures for batracylin and N-acetyl batracylin were near 1. **CONCLUSIONS:** Pharmacogenetically selected patients reached a dose that was 20-fold higher than the MTD in rats and 70 % of the MTD in mice. This genotype-guided strategy was successful in safely delivering batracylin to patients. However, due to unexpected cystitis, not preventable by hydration, and in the absence of a stronger signal for antitumor activity, further development of batracylin has been stopped.

[6]

TÍTULO / TITLE: - NOX4 mediates cytoprotective autophagy induced by the EGFR inhibitor erlotinib in head and neck cancer cells.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Jul 31;272(3):736-745. doi: 10.1016/j.taap.2013.07.013.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.07.013](#)

AUTORES / AUTHORS: - Sobhakumari A; Schickling BM; Love-Homan L; Raeburn A; Fletcher EV; Case AJ; Domann FE; Miller FJ Jr; Simons AL

INSTITUCIÓN / INSTITUTION: - Interdisciplinary Graduate Program in Human Toxicology, The University of Iowa, Iowa City, IA, USA; Department of Pathology, The University of Iowa, Iowa City, IA, USA.

RESUMEN / SUMMARY: - Most head and neck squamous cell carcinomas (HNSCCs) overexpress epidermal growth factor receptor (EGFR) and EGFR inhibitors are routinely used in the treatment of HNSCC. However, many HNSCC tumors do not respond or become refractory to EGFR inhibitors. Autophagy, which is a stress-induced cellular self-degradation process, has been reported to reduce the efficacy of chemotherapy in various disease models. The purpose of this study is to determine if the efficacy of the EGFR inhibitor erlotinib is reduced by activation of autophagy via NOX4-mediated oxidative stress in HNSCC cells. Erlotinib induced the expression of the autophagy marker LC3B-II and autophagosome formation in FaDu and Cal-27 cells. Inhibition of autophagy by chloroquine and knockdown of autophagy pathway genes Beclin-1 and Atg5 sensitized both cell lines to erlotinib-induced cytotoxicity, suggesting that autophagy may serve as a protective mechanism. Treatment with catalase (CAT) and diphenylene iodonium (DPI) in the presence of erlotinib suppressed the increase in LC3B-II expression in FaDu and Cal-27 cells. Erlotinib increased NOX4 mRNA and protein expression by increasing its promoter activity and mRNA stability in FaDu cells. Knockdown of NOX4 using adenoviral siNOX4 partially suppressed erlotinib-induced LC3B-II expression, while overexpression of NOX4 increased expression of LC3B-II. These studies suggest that erlotinib may activate autophagy in HNSCC cells as a pro-survival mechanism, and NOX4 may play a role in mediating this effect.

TÍTULO / TITLE: - The expression of aldehyde dehydrogenase 1 in invasive primary breast tumors and axillary lymph node metastases is associated with poor clinical prognosis.

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

REVISTA / JOURNAL: - Pathol Res Pract. 2013 Sep;209(9):555-61. doi: 10.1016/j.prp.2013.05.007. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) [1016/j.prp.2013.05.007](#)

AUTORES / AUTHORS: - Dong Y; Bi LR; Xu N; Yang HM; Zhang HT; Ding Y; Shi AP; Fan ZM

INSTITUCIÓN / INSTITUTION: - Department of Breast Surgery, First Hospital of Jilin University, Changchun, China.

RESUMEN / SUMMARY: - The enzyme aldehyde dehydrogenase 1 (ALDH1) has been reported as a biomarker for identifying cancer stem cells. Previous studies have shown that ALDH1 expression in primary breast cancers was associated with poor clinical prognosis. In this study, we aimed to determine whether ALDH1 expression in axillary lymph node metastases (ALNM) of breast cancer patients was also associated with poor prognosis. Expression of ALDH1, ER, PgR, HER2 and KI-67 was examined in primary tumors and ALNM of 161 patients with invasive breast cancer. Survival analysis and multivariate analysis were used to determine the relationship between ALDH1 expression and clinical prognosis. Patients with positive ALDH1 expression in primary tumors and in ALNM had significantly shorter relapse-free survival (RFS) times and overall survival (OS) times compared to those whose tissues were ALDH1 negative. ALDH1-positivity in primary tumors was significant both in univariate and multivariate analyses of RFS and OS. ALDH1 expression in ALNM was significant in a univariate analysis of RFS and OS but not in a multivariate analysis of RFS and OS. We conclude that the expression of ALDH1 in primary breast tumors or ALNM may be one potential risk factor for poor, long-term outcomes.

[7]

TÍTULO / TITLE: - Phase II Trial of Bicalutamide in Patients with Androgen Receptor-Positive, Estrogen Receptor-Negative Metastatic Breast Cancer.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5505-5512. Epub 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3327](#)

AUTORES / AUTHORS: - Gucalp A; Tolaney S; Isakoff SJ; Ingle JN; Liu MC; Carey LA; Blackwell K; Rugo H; Nabell L; Forero A; Stearns V; Doane AS; Danso M; Moynahan ME; Momen LF; Gonzalez JM; Akhtar A; Giri DD; Patil S; Feigin KN; Hudis CA; Traina TA

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Breast Cancer Medicine Service, Departments of Pathology, Biostatistics, and Radiology, Memorial Sloan-Kettering Cancer Center; Weill Medical College of Cornell University, New York; Dana-Farber Cancer Institute; Massachusetts General Hospital, Boston, Massachusetts; Mayo Clinic, Rochester, Minnesota; Georgetown Lombardi Comprehensive Cancer Center, Washington, District of Columbia; University of North Carolina at Chapel Hill, Chapel Hill; Duke University Medical Center, Durham, North Carolina; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, UCSF, San Francisco, California; University of Alabama at Birmingham, Birmingham, Alabama; and The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland.

RESUMEN / SUMMARY: - PURPOSE: Patients with hormone receptor-negative breast cancer generally do not benefit from endocrine-targeted therapies. However, a subset with androgen receptor (AR) expression is predicted to respond to antiandrogen

therapies. This phase II study explored bicalutamide in AR-positive, estrogen receptor (ER), and progesterone receptor (PgR)-negative metastatic breast cancer. EXPERIMENTAL DESIGN: Tumors from patients with ER/PgR-negative advanced breast cancer were tested centrally for AR [immunohistochemistry (IHC) > 10% nuclear staining considered positive]. If either the primary or a metastatic site was positive, patients were eligible to receive the AR antagonist bicalutamide at a dose of 150 mg daily. Clinical benefit rate (CBR), the primary endpoint, was defined as the total number of patients who show a complete response (CR), partial response (PR), or stable disease (SD) > 6 months; secondary endpoints included progression-free survival (PFS) and toxicity. Correlative studies included measurement of circulating endocrine markers and IHC surrogates for basal-like breast cancer. RESULTS: Of 424 patients with ER/PgR-negative breast cancer, 12% tested AR-positive. The 6-month CBR was 19% [95% confidence interval (CI), 7%-39%] for bicalutamide. The median PFS was 12 weeks (95% CI, 11-22 weeks). Bicalutamide was well-tolerated with no grade 4/5 treatment-related adverse events observed. CONCLUSION: AR was expressed in 12% of patients with ER/PgR-negative breast cancer screened for this trial. The CBR of 19% observed with bicalutamide shows proof of principle for the efficacy of minimally toxic androgen blockade in a select group of patients with ER/PgR-negative, AR-positive breast cancer. Clin Cancer Res; 19(19); 5505-12. ©2013 AACR.

[8]

TÍTULO / TITLE: - Cetuximab and platinum-based chemoradio- or chemotherapy of patients with epidermal growth factor receptor expressing adenoid cystic carcinoma: a phase II trial.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1117-22. doi: 10.1038/bjc.2013.468. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.468](#)

AUTORES / AUTHORS: - Hitre E; Budai B; Takacs-Nagy Z; Rubovszky G; Toth E; Remenar E; Polgar C; Lang I

INSTITUCIÓN / INSTITUTION: - National Institute of Oncology, Rath Gy. u. 7-9, 1122 Budapest, Hungary.

RESUMEN / SUMMARY: - Background: Epidermal growth factor receptor (EGFR) is highly expressed in adenoid cystic carcinoma (ACC). The efficacy and toxicity of cetuximab with concomitant platinum-based chemoradio- or chemotherapy in patients with locally advanced or metastatic ACC, respectively, was evaluated. Methods: Eligible patients (9 with locally advanced tumour and 12 with metastases) had positive tumour EGFR expression. The cetuximab loading dose (400 mg m⁻²) was followed by 250 mg m⁻² per week. Locally advanced tumours were irradiated (mean dose 65 Gy) and treated with concomitant cisplatin (75 mg m⁻², intravenously). Patients with

metastases received concomitant cisplatin and 5-fluorouracil (4 x 1000 mg m(-2)). Results: For patients with locally advanced disease (median follow-up: 52 months), the median progression-free survival (PFS) was 64 months and the 2-year overall survival (OS) rate was 100%. For patients with metastases (median follow-up: 72 months), the median PFS and OS were 13 and 24 months, respectively. In both groups the objective response rate was >40%. Skin rash, in-field dermatitis, mucositis and vomiting were the most frequent grade 3/4 adverse events. Conclusion: In this single-arm study, the efficacy of cetuximab plus chemoradio- or chemotherapy appeared favourable as compared with historical controls. All side effects were manageable and did not hamper the treatment.

[9]

TÍTULO / TITLE: - Inhibition of mTORC1 by Astrin and Stress Granules Prevents Apoptosis in Cancer Cells.

RESUMEN / SUMMARY: -

ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23953116

●● Enlace al texto completo (gratis o de pago) [1016/j.cell.2013.07.031](https://doi.org/10.1016/j.cell.2013.07.031)

AUTORES / AUTHORS: - Thedieck K; Holzwarth B; Prentzell MT; Boehlke C; Klasener K; Ruf S; Sonntag AG; Maerz L; Grellscheid SN; Kremmer E; Nitschke R; Kuehn EW; Jonker JW; Groen AK; Reth M; Hall MN; Baumeister R

INSTITUCIÓN / INSTITUTION: - Faculty of Biology, Albert-Ludwigs-University Freiburg, 79104 Freiburg, Germany; Bioinformatics and Molecular Genetics, Faculty of Biology, Albert-Ludwigs-University Freiburg, 79104 Freiburg, Germany; BIOS Centre for Biological Signalling Studies, Albert-Ludwigs-University Freiburg, 79104 Freiburg, Germany; Center for Systems Biology (ZBSA), Albert-Ludwigs-University Freiburg, 79104 Freiburg, Germany; Renal Division, University Hospital Freiburg, 79106 Freiburg, Germany. Electronic address: k.thedieck@umcg.nl.

RESUMEN / SUMMARY: - Mammalian target of rapamycin complex 1 (mTORC1) controls growth and survival in response to metabolic cues. Oxidative stress affects mTORC1 via inhibitory and stimulatory inputs. Whereas downregulation of TSC1-TSC2 activates mTORC1 upon oxidative stress, the molecular mechanism of mTORC1 inhibition remains unknown. Here, we identify astrin as an essential negative mTORC1 regulator in the cellular stress response. Upon stress, astrin inhibits mTORC1 association and recruits the mTORC1 component raptor to stress granules (SGs), thereby preventing mTORC1-hyperactivation-induced apoptosis. In turn, balanced mTORC1 activity enables expression of stress factors. By identifying astrin as a direct molecular link between mTORC1, SG assembly, and the stress response, we establish a unifying model of mTORC1 inhibition and activation upon stress. Importantly, we show that in cancer cells, apoptosis suppression during stress depends on astrin. Being frequently

upregulated in tumors, astrin is a potential clinically relevant target to sensitize tumors to apoptosis.

[10]

TÍTULO / TITLE: - Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt375](#)

AUTORES / AUTHORS: - Procopio G; Verzoni E; Bracarda S; Ricci S; Sacco C; Ridolfi L; Porta C; Miceli R; Zilembo N; Bajetta E

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan.

RESUMEN / SUMMARY: - BACKGROUND: The ROSORC trial, a randomised, phase II trial comparing sorafenib plus interleukin (IL-2) versus sorafenib alone as first-line treatment of metastatic renal cell carcinoma (mRCC) failed to demonstrate differences in progression-free survival (PFS). Updated overall survival (OS) results are reported. PATIENTS AND METHODS: In this study, 128 patients were randomised to receive sorafenib 400 mg twice daily plus subcutaneous IL-2 4.5 million international units (MIU) five times per week for 6 weeks every 8 weeks (arm A) or sorafenib alone (arm B). OS was estimated with the Kaplan-Meier method and compared with the two-sided log-rank test. RESULTS: After a median follow-up of 58 months (interquartile range: 28-63 months), the median OS was 38 and 33 months in arms A and B, respectively (P = 0.667). The 5-year OS was 26.3% [95% confidence interval (CI) 15.9-43.5] and 23.1% (95% CI 13.2-40.5) for the combination- and single-agent arm, respectively. Most of the patients who were refractory to first-line treatment were subsequently treated with different targeted agents; they had a median survival greater than expected. CONCLUSIONS: This outcome suggests a synergistic effect of the subsequent therapies following sorafenib failure. CLINICALTRIALS.GOV IDENTIFIER: NCT00609401.

TÍTULO / TITLE: - Activity ex vivo of cytotoxic drugs in patient samples of peritoneal carcinomatosis with special focus on colorectal cancer.

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

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 24;13(1):435.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-435](#)

AUTORES / AUTHORS: - Mahteme H; Graf W; Karlsson H; Larsson R; Nygren P

RESUMEN / SUMMARY: - BACKGROUND: The optimal choice of cytotoxic drugs for intraperitoneal chemotherapy (IPC) in conjunction with cytoreductive surgery (CRS) for

treatment of peritoneal carcinomatosis (PC) is poorly defined. We investigated drug sensitivity ex vivo in patient samples of various PC tumor types and correlated clinical outcome to drug sensitivity within the subset of PC from colorectal cancer (CRC). METHODS: PC tissue samples (n = 174) from mesothelioma, pseudomyxoma peritonei (PMP), ovarian cancer, CRC or appendix cancer were analyzed ex vivo for sensitivity to oxaliplatin, cisplatin, mitomycin C, melphalan, irinotecan, docetaxel, doxorubicin and 5-FU. Clinicopathological variables and outcome data were collected for the CRC subset. RESULTS: Mesothelioma and ovarian cancer were generally more drug sensitive than CRC, appendix cancer and PMP. Oxaliplatin showed the most favorable ratio between achievable IPC concentration and ex vivo drug sensitivity. Drug sensitivity in CRC varied considerably between individual samples. Ex vivo drug sensitivity did not obviously correlate to time-to-progression (TTP) in individual patients. CONCLUSIONS: Drug-sensitivity varies considerably between PC diagnoses and individual patients arguing for individualized therapy in IPC rather than standard diagnosis-specific therapy. However, in the current paradigm of treatment according to diagnosis, oxaliplatin is seemingly the preferred drug for IPC from a drug sensitivity and concentration perspective. In the CRC subset, analysis of correlation between ex vivo drug sensitivity and TTP was inconclusive due to the heterogeneous nature of the data.

[11]

TÍTULO / TITLE: - Smudge cells following treatment with pentostatin in a patient with B-cell prolymphocytic leukemia.

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

REVISTA / JOURNAL: - Blood. 2013 Jul 25;122(4):474.

AUTORES / AUTHORS: - Yun HD; Waller EK

[12]

TÍTULO / TITLE: - Identification of gene expression-based prognostic markers in the hematopoietic stem cells of patients with myelodysplastic syndromes.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Oct 1;31(28):3557-64. doi: 10.1200/JCO.2012.45.5626. Epub 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.45.5626](#)

AUTORES / AUTHORS: - Pellagatti A; Benner A; Mills KI; Cazzola M; Giagounidis A; Perry J; Malcovati L; Della Porta MG; Jadersten M; Verma A; McDonald EJ; Killick S; Hellstrom-Lindberg E; Bullinger L; Wainscoat JS; Boulwood J

INSTITUCIÓN / INSTITUTION: - Andrea Pellagatti, Janet Perry, James S. Wainscoat, and Jacqueline Boulwood, University of Oxford, Oxford; Ken I. Mills, Queen's University Belfast, Belfast; Emma-Jane McDonald and Sally Killick, Royal Bournemouth Hospital,

Bournemouth, United Kingdom; Axel Benner, German Cancer Research Center, Heidelberg; Aristoteles Giagounidis, St Johannes Hospital, Duisburg; Lars Bullinger, University Hospital of Ulm, Ulm, Germany; Mario Cazzola, Luca Malcovati, and Matteo G. Della Porta, Fondazione Istituto di Ricovera e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; Martin Jadersten and Eva Hellstrom-Lindberg, Karolinska Institutet, Stockholm, Sweden; and Amit Verma, Albert Einstein College of Medicine, New York, NY.

RESUMEN / SUMMARY: - PURPOSE: The diagnosis of patients with myelodysplastic syndromes (MDS) is largely dependent on morphologic examination of bone marrow aspirates. Several criteria that form the basis of the classifications and scoring systems most commonly used in clinical practice are affected by operator-dependent variation. To identify standardized molecular markers that would allow prediction of prognosis, we have used gene expression profiling (GEP) data on CD34+ cells from patients with MDS to determine the relationship between gene expression levels and prognosis. PATIENTS AND METHODS: GEP data on CD34+ cells from 125 patients with MDS with a minimum 12-month follow-up since date of bone marrow sample collection were included in this study. Supervised principal components and lasso penalized Cox proportional hazards regression (Coxnet) were used for the analysis. RESULTS: We identified several genes, the expression of which was significantly associated with survival of patients with MDS, including LEF1, CDH1, WT1, and MN1. The Coxnet predictor, based on expression data on 20 genes, outperformed other predictors, including one that additionally used clinical information. Our Coxnet gene signature based on CD34+ cells significantly identified a separation of patients with good or bad prognosis in an independent GEP data set based on unsorted bone marrow mononuclear cells, demonstrating that our signature is robust and may be applicable to bone marrow cells without the need to isolate CD34+ cells. CONCLUSION: We present a new, valuable GEP-based signature for assessing prognosis in MDS. GEP-based signatures correlating with clinical outcome may significantly contribute to a refined risk classification of MDS.

[13]

TÍTULO / TITLE: - Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial.

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

REVISTA / JOURNAL: - Lancet Oncol. 2013 Sep;14(10):989-98. doi: 10.1016/S1470-2045(13)70322-X. Epub 2013 Jul 29.

●● Enlace al texto completo (gratis o de pago) [1016/S1470-2045\(13\)70322-X](#)

AUTORES / AUTHORS: - Johnston SR; Kilburn LS; Ellis P; Dodwell D; Cameron D; Hayward L; Im YH; Braybrooke JP; Brunt AM; Cheung KL; Jyothirmayi R; Robinson A; Wardley AM; Wheatley D; Howell A; Coombes G; Sergenson N; Sin HJ; Folkerd E; Dowsett M; Bliss JM

INSTITUCIÓN / INSTITUTION: - Royal Marsden NHS Foundation Trust, London, UK.

Electronic address: stephen.johnston@rmh.nhs.uk.

RESUMEN / SUMMARY: - **BACKGROUND:** The optimum endocrine treatment for postmenopausal women with advanced hormone-receptor-positive breast cancer that has progressed on non-steroidal aromatase inhibitors (NSAIs) is unclear. The aim of the SoFEA trial was to assess a maximum double endocrine targeting approach with the steroidal anti-oestrogen fulvestrant in combination with continued oestrogen deprivation. **METHODS:** In a composite, multicentre, phase 3 randomised controlled trial done in the UK and South Korea, postmenopausal women with hormone-receptor-positive breast cancer (oestrogen receptor [ER] positive, progesterone receptor [PR] positive, or both) were eligible if they had relapsed or progressed with locally advanced or metastatic disease on an NSAI (given as adjuvant for at least 12 months or as first-line treatment for at least 6 months). Additionally, patients had to have adequate organ function and a WHO performance status of 0-2. Participants were randomly assigned (1:1:1) to receive fulvestrant (500 mg intramuscular injection on day 1, followed by 250 mg doses on days 15 and 29, and then every 28 days) plus daily oral anastrozole (1 mg); fulvestrant plus anastrozole-matched placebo; or daily oral exemestane (25 mg). Randomisation was done with computer-generated permuted blocks, and stratification was by centre and previous use of an NSAI as adjuvant treatment or for locally advanced or metastatic disease. Participants and investigators were aware of assignment to fulvestrant or exemestane, but not of assignment to anastrozole or placebo. The primary endpoint was progression-free survival (PFS). Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, numbers NCT00253422 (UK) and NCT00944918 (South Korea). **FINDINGS:** Between March 26, 2004, and Aug 6, 2010, 723 patients underwent randomisation: 243 were assigned to receive fulvestrant plus anastrozole, 231 to fulvestrant plus placebo, and 249 to exemestane. Median PFS was 4.4 months (95% CI 3.4-5.4) in patients assigned to fulvestrant plus anastrozole, 4.8 months (3.6-5.5) in those assigned to fulvestrant plus placebo, and 3.4 months (3.0-4.6) in those assigned to exemestane. No difference was recorded between the patients assigned to fulvestrant plus anastrozole and fulvestrant plus placebo (hazard ratio 1.00, 95% CI 0.83-1.21; log-rank p=0.98), or between those assigned to fulvestrant plus placebo and exemestane (0.95, 0.79-1.14; log-rank p=0.56). 87 serious adverse events were reported: 36 in patients assigned to fulvestrant plus anastrozole, 22 in those assigned to fulvestrant plus placebo, and 29 in those assigned to exemestane. Grade 3-4 adverse events were rare; the most frequent were arthralgia (three in the group assigned to fulvestrant plus anastrozole; seven in that assigned to fulvestrant plus

placebo; eight in that assigned to exemestane), lethargy (three; 11; 11), and nausea or vomiting (five; two; eight). INTERPRETATION: After loss of response to NSAIs in postmenopausal women with hormone-receptor-positive advanced breast cancer, maximum double endocrine treatment with 250 mg fulvestrant combined with oestrogen deprivation is no better than either fulvestrant alone or exemestane. FUNDING: Cancer Research UK and AstraZeneca.

[14]

TÍTULO / TITLE: - Effect of leuprolide acetate on ovarian function after cyclophosphamide-doxorubicin-based chemotherapy in premenopausal patients with breast cancer: results from a phase II randomized trial.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):667. doi: 10.1007/s12032-013-0667-8. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0667-8](#)

AUTORES / AUTHORS: - Song G; Gao H; Yuan Z

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Jiangyin Hospital Affiliated to Nanjing University of Traditional Chinese Medicine, Jiangyin, Jiangsu, China.

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RESUMEN / SUMMARY: - Previous studies provided inconclusive evidence for the effectiveness of gonadotropin-releasing hormone analogue on ovarian function protection against chemotherapy-induced genotoxicity in premenopausal patients. This study was designed to examine the efficacy of leuprolide acetate on ovarian function preservation in patients with breast cancer. A total of 220 patients were recruited in this prospective clinical trial and were assigned randomly to receive cyclophosphamide-doxorubicin-based chemotherapy only or chemotherapy plus leuprolide acetate. Resumption of menses or premenopausal levels of both follicle-stimulating hormone (FSH) and estradiol (E2) within 12 months after the end of chemotherapy were considered as effective ovarian preservation. A total of 183 patients were considered evaluable (94 in chemotherapy-only group and 89 in chemotherapy plus leuprolide acetate group). At the end of follow-up, 27 patients in chemotherapy group and 15 in chemotherapy plus leuprolide acetate group resumed menses; seven patients in chemotherapy group and 14 in chemotherapy plus leuprolide acetate group restored premenopausal levels of FSH and E2. The median time to resume menses was 9.2 months for patients in chemotherapy plus leuprolide acetate group and was not reached in chemotherapy-only group. In addition, our results demonstrated that age and chemotherapy doses made no significant difference in the occurrence of premature menopause. The leuprolide acetate treatment simultaneously with cyclophosphamide-doxorubicin-based chemotherapy reduced the

risk of developing premature menopause in premenopausal patients with breast cancer.

[15]

TÍTULO / TITLE: - Egress of CD19+CD5+ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients.

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

REVISTA / JOURNAL: - Blood. 2013 Oct 3;122(14):2412-2424. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-02-482125](#)

AUTORES / AUTHORS: - Chang BY; Francesco M; De Rooij MF; Magadala P; Steggerda SM; Huang MM; Kuil A; Herman SE; Chang S; Pals ST; Wilson W; Wiestner A; Spaargaren M; Buggy JJ; Elias L

INSTITUCIÓN / INSTITUTION: - Research Department, Pharmacyclics, Inc., Sunnyvale, CA;

RESUMEN / SUMMARY: - Ibrutinib (PCI-32765) is a highly potent oral Bruton tyrosine kinase (BTK) inhibitor in clinical development for treating B-cell lymphoproliferative diseases. Patients with chronic lymphocytic leukemia (CLL) often show marked, transient increases of circulating CLL cells following ibrutinib treatments, as seen with other inhibitors of the B-cell receptor (BCR) pathway. In a phase 1 study of ibrutinib, we noted similar effects in patients with mantle cell lymphoma (MCL). Here, we characterize the patterns and phenotypes of cells mobilized among patients with MCL and further investigate the mechanism of this effect. Peripheral blood CD19+CD5+ cells from MCL patients were found to have significant reduction in the expression of CXCR4, CD38, and Ki67 after 7 days of treatment. In addition, plasma chemokines such as CCL22, CCL4, and CXCL13 were reduced 40% to 60% after treatment.

Mechanistically, ibrutinib inhibited BCR- and chemokine-mediated adhesion and chemotaxis of MCL cell lines and dose-dependently inhibited BCR, stromal cell, and CXCL12/CXCL13 stimulations of pBTK, pPLCgamma2, pERK, or pAKT. Importantly, ibrutinib inhibited migration of MCL cells beneath stromal cells in coculture. We propose that BTK is essential for the homing of MCL cells into lymphoid tissues, and its inhibition results in an egress of malignant cells into peripheral blood. This trial was registered at www.clinicaltrials.gov as #NCT00114738.

[16]

TÍTULO / TITLE: - Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Aug 28. pii: S0169-5002(13)00381-4. doi: 10.1016/j.lungcan.2013.08.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.08.016](#)

AUTORES / AUTHORS: - Iuchi T; Shingyoji M; Sakaida T; Hatano K; Nagano O; Itakura M; Kageyama H; Yokoi S; Hasegawa Y; Kawasaki K; Iizasa T

INSTITUCIÓN / INSTITUTION: - Divisions of Neurological Surgery, Chiba Cancer Center, Chiba, Japan. Electronic address: tiuchi@chiba-c.jp.

RESUMEN / SUMMARY: - BACKGROUND: Brain metastases (BM) are a common in patients with lung cancer. Although whole-brain radiation therapy (WBRT) is the standard therapy, it may have a risk of decline in cognitive function of patients. In this study, we evaluated the efficacy of gefitinib alone without radiation therapy for the treatment of patients with BM from lung adenocarcinoma. MATERIALS AND METHODS: Eligible patients had BM from lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations. Gefitinib was given at 250mg orally once a day until tumor progression or unacceptable toxicity. RESULTS: Forty-one patients were enrolled. The response rate was 87.8%. No patient experienced grade ≥ 4 toxicity. The median progression-free survival time was 14.5 months (95% CI, 10.2-18.3 months), and the median overall survival time was 21.9 months (95% CI, 18.5-30.3 months). In compared with L858R, exon 19 deletion was associated with better outcome of patients after treatment with gefitinib in both progression-free ($p=0.003$) and overall survival ($p=0.025$). CONCLUSION: Favorable response of BM to gefitinib even without irradiation was demonstrated. Exon 19 deletion was both a predictive and prognostic marker of patients with BM treated by gefitinib.

[17]

TÍTULO / TITLE: - A randomized, open-label, phase I/II trial to investigate the maximum tolerated dose of the Polo-like kinase inhibitor BI 2536 in elderly patients with refractory/relapsed acute myeloid leukaemia.

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

REVISTA / JOURNAL: - Br J Haematol. 2013 Aug 16. doi: 10.1111/bjh.12518.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12518](#)

AUTORES / AUTHORS: - Muller-Tidow C; Bug G; Lubbert M; Kramer A; Krauter J; Valent P; Nachbaur D; Berdel WE; Ottmann OG; Fritsch H; Munzert G; Garin-Chesa P; Fleischer F; Taube T; Dohner H

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Haematology and Oncology, University of Munster, Munster, Germany.

RESUMEN / SUMMARY: - Polo-like kinases (Plks) play an important role in cell cycle checkpoint controls and are over-expressed in acute myeloid leukaemia (AML). BI 2536, a novel Plk inhibitor, induces mitotic arrest and apoptosis. In this phase I/II trial of BI 2536 in 68 elderly patients with relapsed/refractory AML, three schedules were investigated (day 1, days 1-3, and days 1 + 8). Maximum tolerated dose was 350 and 200 mg in the day 1 and days 1 + 8 schedules, respectively. The day 1-3 schedule appeared equivalent to the day 1 schedule and was discontinued early. BI 2536

exhibited multi-compartmental pharmacokinetic behaviour. The majority of patients showed an increase of bone marrow cells in G2/M with a characteristic pattern of mitotic catastrophe. The overall response rate in the day 1 and day 1 + 8 schedules was 9% (5/54) with 2 complete and 3 partial responses. The majority of drug-related adverse events grade ≥ 3 were haematological. Taken together, Plk inhibition induced cell cycle arrest in AML blasts in vivo and BI 2536 monotherapy showed modest clinical activity in this poor prognosis patient group.

[18]

TÍTULO / TITLE: - Re: Long-term follow-up of a phase II trial of chemotherapy plus hormone therapy for biochemical relapse after definitive local therapy for prostate cancer.

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

REVISTA / JOURNAL: - J Urol. 2013 Sep;190(3):880. doi: 10.1016/j.juro.2013.05.105. Epub 2013 Jun 7.

●● Enlace al texto completo (gratis o de pago) 1016/j.juro.2013.05.105

AUTORES / AUTHORS: - Taneja SS

[19]

TÍTULO / TITLE: - Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment in Patients With EGFR Wild-Type Non-Small-Cell Lung Cancer: The Never-Ending Story.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 10;31(26):3291-3. doi: 10.1200/JCO.2013.50.2617. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) 1200/JCO.2013.50.2617

AUTORES / AUTHORS: - Gelsomino F; Agostoni F; Nigam M; Valota M; Haslinger ER

INSTITUCIÓN / INSTITUTION: - Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy.

[20]

TÍTULO / TITLE: - Polymorphisms in DNA repair and apoptosis-related genes and clinical outcomes of patients with non-small cell lung cancer treated with first-line paclitaxel-cisplatin chemotherapy.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Aug 8. pii: S0169-5002(13)00333-4. doi: 10.1016/j.lungcan.2013.07.024.

●● Enlace al texto completo (gratis o de pago) 1016/j.lungcan.2013.07.024

AUTORES / AUTHORS: - Lee SY; Kang HG; Yoo SS; Kang YR; Choi YY; Lee WK; Choi JE; Jeon HS; Shin KM; Oh IJ; Kim KS; Lee J; Cha SI; Kim CH; Kim YC; Park JY

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea.

RESUMEN / SUMMARY: - This study was conducted to analyze a comprehensive panel of single nucleotide polymorphisms (SNPs) in genes in DNA repair and apoptosis pathways and determine the relationship between polymorphisms and treatment outcomes of patients with non-small cell lung cancer (NSCLC) treated with first-line paclitaxel-cisplatin chemotherapy. Three hundred eighty two patients with NSCLC were enrolled. Seventy-four SNPs in 48 genes (42 SNPs in 27 DNA repair pathway genes and 32 SNPs in 21 apoptotic pathway genes) were genotyped and their associations with chemotherapy response and overall survival (OS) were analyzed. Among SNPs in DNA repair genes, BRCA1 rs799917 was significantly associated with both chemotherapy response and OS. XRCC1 rs25487 exhibited a significant association with chemotherapy response and ERCC2 rs1052555 with OS. Four SNPs in apoptotic genes (TNFRSF1B rs1061624, BCL2 rs2279115, BIRC5 rs9904341, and CASP8 rs3769818) were significantly associated with OS, but not with response to chemotherapy. When the six SNPs which were associated with OS in individual analysis were combined, OS decreased as the number of bad genotypes increased (Ptrend=2x10⁻⁶). Patients with 3, and 4-6 bad genotypes had significantly worse OS compared with those carrying 0-2 bad genotypes (adjusted hazard ratio [aHR]=1.54, 95% CI=1.14-2.08, P=0.005; aHR=2.10, 95% CI=1.55-2.85, P=2x10⁻⁶, respectively). In conclusion, these findings suggest that the six SNPs identified, particularly their combined genotypes, could be used as biomarkers predicting chemotherapy response and survival of NSCLC patients treated with first-line paclitaxel-cisplatin chemotherapy.

[21]

TÍTULO / TITLE: - Adjuvant Aromatase Inhibitor Therapy in Patients with Stage I Breast Cancer at a Regional Oncology Center in Israel: Implementation of a 'Switching' Policy in Postmenopausal Patients after Initial Tamoxifen.

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

REVISTA / JOURNAL: - Oncology. 2013 Aug 28;85(3):145-152.

●● Enlace al texto completo (gratis o de pago) [1159/000353978](#)

AUTORES / AUTHORS: - Geffen DB; Tokar M; Abu-Ghanem S; Braunstein R; Koretz M; Amir N; Delgado B; Sion-Vardi N; Ariad S; Lazarev I

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel.

RESUMEN / SUMMARY: - Objective: To analyze the implementation of a switching policy of adjuvant aromatase inhibitor (AI) therapy sequentially after tamoxifen in consecutively treated stage I (T1N0M0) hormone receptor (HR)-positive breast cancer

(BC) patients. Methods: The records of 279 consecutive HR-positive BC patients diagnosed between 2002 and 2006 and followed at the Soroka Medical Center were reviewed. Results: Two-hundred-seventeen patients who initially received tamoxifen were suitable for switching and 28 received an AI as initial adjuvant treatment. The switch was accomplished in 82.5% of the 217 patients. Those who switched to an AI had a higher proportion of T1c stage than patients eligible who were not switched, but did not differ in age, histologic grade, or having received chemotherapy. Of the 179 patients who switched, 155 (86.6%) completed at least 4.5-5 years of adjuvant tamoxifen/AI therapy. Eighteen patients discontinued AI therapy prematurely because of toxicity. Conclusions: In this stage I BC population, despite the toxicities of AI therapy, >84% of eligible patients received an AI as adjuvant therapy. Measures to improve the management of AI toxicity, such as changing to a different AI, may reduce early stopping.

[22]

TÍTULO / TITLE: - How to Incorporate New Tyrosine Kinase Inhibitors in the Treatment of Patients With Medullary Thyroid Cancer.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2013.51.5098](#)

AUTORES / AUTHORS: - Haddad RI

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

[23]

TÍTULO / TITLE: - Molecular and clinical risk factors for recurrence of skull base chordomas: gain on chromosome 2p, expression of brachyury, and lack of irradiation negatively correlate with patient prognosis.

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

REVISTA / JOURNAL: - J Neuropathol Exp Neurol. 2013 Sep;72(9):816-23. doi: 10.1097/NEN.0b013e3182a065d0.

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

[1097/NEN.0b013e3182a065d0](#)

AUTORES / AUTHORS: - Kitamura Y; Sasaki H; Kimura T; Miwa T; Takahashi S; Kawase T; Yoshida K

INSTITUCIÓN / INSTITUTION: - From the Departments of Neurosurgery (YK, HS, TM, ST, TKawase, KY), and Pathology (TKimura), Keio University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - Chordomas are invasive tumors that develop from notochordal remnants and frequently occur in the skull base. The T gene and its product (brachyury) have recently been suggested to play an important role in chordoma progression. To date, few studies have investigated the relationship between the molecular/genetic characteristics of chordoma and patient prognosis. We analyzed 37 skull base chordomas for chromosomal copy number aberrations using comparative genomic hybridization, brachyury expression by immunohistochemistry, and T gene copy number by fluorescence in situ hybridization. The results of these molecular analyses and clinical parameters were compared with the patients' clinical courses. Univariate analyses using the log-rank test demonstrated that losses on chromosome 1p and gains on 1q and 2p were negatively correlated with progression-free survival, as were factors such as female sex, partial tumor removal, lack of postoperative irradiation, and high MIB-1 index. Expression of brachyury and copy number gain of the T gene were also significantly associated with shorter progression-free survival. Multivariate analysis using the Cox hazards model showed that lack of irradiation, gain on chromosome 2p, and expression of brachyury were independently associated with a poor prognosis. Our results suggest that brachyury-negative chordomas are biologically distinct from brachyury-positive chordomas and that T/brachyury might be an appropriate molecular therapeutic target for chordoma.

[24]

TÍTULO / TITLE: - Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): Important lessons for future trials.

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

REVISTA / JOURNAL: - Cancer. 2013 Aug 13. doi: 10.1002/cncr.28270.

●● [Enlace al texto completo \(gratis o de pago\) 1002/cncr.28270](#)

AUTORES / AUTHORS: - Schweizer MT; Huang P; Kattan MW; Kibel AS; de Wit R; Sternberg CN; Epstein JI; Eisenberger MA

INSTITUCIÓN / INSTITUTION: - Prostate Cancer Research Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland.

RESUMEN / SUMMARY: - **BACKGROUND:** The current trial evaluated 2 common therapies for patients with advanced prostate cancer, docetaxel and hormonal therapy (HT), in the surgical adjuvant setting. **METHODS:** TAX-3501 was a randomized, phase 3, adjuvant study post-radical prostatectomy (RP) in high-risk patients with prostate cancer (n = 228) comparing 18 months of HT with (CHT) without docetaxel chemotherapy either immediately (I) or deferred (D). High-risk disease was defined as a 5-year freedom-from-disease-progression rate of $\leq 60\%$ as predicted by a post-RP nomogram. Progression-free survival (PFS), including prostate-specific antigen disease recurrence, was the primary endpoint. The authors also assessed the accuracy of the

nomogram and analyzed testosterone recovery in 108 patients treated with HT who had at least 1 posttreatment testosterone value. RESULTS: Between December 2005 and September 2007, 228 patients were randomized between the treatment cohorts. TAX-3501 was terminated prematurely because of enrollment challenges, leaving it underpowered to detect differences in PFS. After a median follow-up of 3.4 years (interquartile range, 2.3-3.8 years), 39 of 228 patients (17%) demonstrated PSA disease progression, and metastatic disease progression occurred in 1 patient. The median time to baseline testosterone recovery after the completion of treatment was prolonged at 487 days (95% confidence interval, 457-546 days). The nomogram's predicted versus observed freedom from disease progression was significantly different for the combination D(HT) and D(HT) group ($P < .00001$). CONCLUSIONS: TAX-3501 illustrated several difficulties involved in conducting postoperative adjuvant systemic trials in men with high-risk prostate cancer: the lack of consensus regarding patient selection and treatment, the need for long follow-up time, nonvalidated intermediate endpoints, evolving standard approaches, and the need for long-term research support. Except for selected patients at very high-risk of disease recurrence and death, surgical adjuvant trials in patients with prostate cancer may not be feasible. Cancer 2013. © 2013 American Cancer Society.

[25]

TÍTULO / TITLE: - Primary Esophageal Cancer: Heterogeneity as Potential Prognostic Biomarker in Patients Treated with Definitive Chemotherapy and Radiation Therapy.

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

REVISTA / JOURNAL: - Radiology. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) 1148/radiol.13122869

AUTORES / AUTHORS: - Yip C; Landau D; Kozarski R; Ganeshan B; Thomas R; Michaelidou A; Goh V

INSTITUCIÓN / INSTITUTION: - Departments of Oncology and Radiology, Guy's and St Thomas' National Health Service Foundation Trust, Lower Ground Floor, Lambeth Wing, Westminster Bridge Road, London SE1 7EH, England; Centre for Lifespan and Chronic Illness Research, University of Hertfordshire, Hatfield, England; Institute of Nuclear Medicine, University College London, London, England.

RESUMEN / SUMMARY: - Purpose: To determine the association between tumor heterogeneity, morphologic tumor response, and overall survival in primary esophageal cancer treated with chemotherapy and radiation therapy (CRT). Materials and Methods: After an institutional review board waiver was obtained, contrast material-enhanced computed tomographic (CT) studies in 36 patients with stage T2 or greater esophageal tumors who underwent contrast-enhanced CT before and after CRT between 2005 and 2008 were analyzed in terms of whole-tumor texture, with quantification of entropy, uniformity, mean gray-level intensity, kurtosis, standard

deviation of the histogram, and skewness for fine to coarse textures (filters 1.0-2.5, respectively). The association between texture parameters and survival time was assessed by using Kaplan-Meier analysis and a Cox proportional hazards model. Survival models involving texture parameters and combinations of texture and morphologic response assessment were compared with morphologic assessment alone by means of receiver operating characteristic (ROC) analysis. Results: Posttreatment medium entropy of less than 7.356 (median overall survival, 33.2 vs 11.7 months; $P = .0002$), coarse entropy of less than 7.116 (median overall survival, 33.2 vs 11.7 months; $P = .0002$), and medium uniformity of 0.007 or greater (median overall survival, 33.2 vs 11.7 months; $P = .0002$) were associated with improved survival time. These remained significant prognostic factors after adjustment for stage and age: entropy (filter 2.0: hazard ratio [HR] = 5.038, $P = .0004$; filter 2.5: HR = 5.038, $P = .0004$) and uniformity (HR = 0.199, $P = .0004$). Survival models that included a combination of pretreatment entropy and uniformity with maximal wall thickness assessment, respectively, performed better than morphologic assessment alone (area under the ROC curve, 0.767 vs 0.487 [$P = .00005$] and 0.802 vs 0.487 [$P = .0003$]). Conclusion: Posttreatment texture parameters are associated with survival time, and the combination of pretreatment texture parameters and maximal wall thickness performed better in survival models than morphologic tumor response alone. © RSNA, 2013 Supplemental material:

<http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13122869/-/DC1>.

[26]

TÍTULO / TITLE: - Impact of c-MYC Protein Expression on Outcome of Patients with Early-Stage HER2+ Breast Cancer Treated with Adjuvant Trastuzumab NCCTG (Alliance) N9831.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0558](#)

AUTORES / AUTHORS: - Dueck AC; Reinholz MM; Geiger XJ; Tenner KS; Ballman KV; Jenkins RB; Riehle D; Chen B; McCullough AE; Davidson NE; Martino S; Sledge GW; Kaufman PA; Kutteh LA; Gralow J; Harris L; Ingle JN; Lingle W; Perez EA

INSTITUCIÓN / INSTITUTION: - Section of Biostatistics, Mayo Clinic, Arizona.

RESUMEN / SUMMARY: - PURPOSE: This study investigated the association between tumor MYC protein expression and disease-free survival (DFS) of patients randomized to receive chemotherapy alone (Arm A) or chemotherapy with sequential (Arm B) or concurrent trastuzumab (Arm C) in the N9831 (Alliance) adjuvant HER2+ trastuzumab breast cancer trial. EXPERIMENTAL DESIGN: This analysis included 1736 patients randomized to Arms A, B, and C on N9831. Nuclear MYC protein expression was determined in tissue microarray (TMA) sections containing three biopsies per patient

or whole tissue sections (WS) using standard immunohistochemistry (clone 9E10). A tumor was considered positive for MYC protein overexpression (MYC+) if the nuclear 3+ staining percentage was >30%. RESULTS: 574 (33%) tumors were MYC+. MYC+ was associated with hormone receptor positivity (chi2 p=0.006), tumors \geq 2 cm (chi2 p=0.02), and a higher rate of nodal positivity (chi2 p<0.001). Hazard ratios (HRs) for DFS (median follow-up: 6.1 years) for Arm C versus A were 0.52 (p=0.006) and 0.65 (p=0.006) for patients with MYC+ and MYC- tumors, respectively (interaction p=0.40). For Arm B versus A, HRs for patients with MYC+ and MYC- tumors were 0.79 (p=0.21) and 0.74 (p=0.04), respectively (interaction p=0.71). For Arm C versus B, HRs for patients with MYC+ and MYC- tumors were 0.56 (p=0.02) and 0.89 (p=0.49), respectively (interaction p=0.17). CONCLUSIONS: Our data do not support an impact of tumor MYC protein expression on differential benefit from adjuvant trastuzumab.

[27]

TÍTULO / TITLE: - Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 8. pii: S0959-8049(13)00491-7. doi: 10.1016/j.ejca.2013.06.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.06.016](#)

AUTORES / AUTHORS: - Trovik J; Wik E; Werner HM; Krakstad C; Helland H; Vandepuit I; Njolstad TS; Stefansson IM; Marcickiewicz J; Tingulstad S; Staff AC; Amant F; Akslen LA; Salvesen HB

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway. Electronic address: jone.trovik@helse-bergen.no.

RESUMEN / SUMMARY: - BACKGROUND: Preoperative histologic examination of tumour tissue is essential when deciding if endometrial cancer surgery should include lymph node sampling. We wanted to investigate if biomarkers could improve prediction of lymph node metastasis and outcome. PATIENTS AND METHODS: Curettage specimens from 832 endometrial carcinoma patients prospectively recruited from 10 centres in the MoMaTEC trial (Molecular Markers in Treatment of Endometrial Cancer) were investigated for hormone receptor and p53 status. RESULTS: Eighteen per cent of tumours were double negative for oestrogen- and progesterone receptors (ER/PR loss), 24% overexpressed p53. Pathologic expression of all markers correlated with nodal metastases, high FIGO (Federation International of Gynecology and Obstetrics) stage, non-endometrioid histology, high grade and poor prognosis (all P<0.001). ER/PR loss independently predicted lymph node metastasis (odds ratios (OR) 2.0, 95% confidence interval (CI) 1.1-3.7) adjusted for preoperative curettage histology and predicted poor disease-specific survival adjusted for age, FIGO stage, histologic type,

grade and myometrial infiltration (hazard ratio (HR) 2.3, 95% CI 1.4-3.9). For lymph node negative endometrioid tumours, ER/PR loss influenced survival independent of grade. CONCLUSION: Double negative hormone receptor status in endometrial cancer curettage independently predicts lymph node metastasis and poor prognosis in a prospective multicentre setting. Implementing hormone receptor status to improve risk-stratification for selecting patients unlikely to benefit from lymphadenectomy seems justified.

[28]

TÍTULO / TITLE: - Gene expression profile of A549 cells from tissue of 4D model predicts poor prognosis in lung cancer patients.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 12. doi: 10.1002/ijc.28428.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28428](#)

AUTORES / AUTHORS: - Mishra DK; Creighton CJ; Zhang Y; Gibbons DL; Kurie JM; Kim MP

INSTITUCIÓN / INSTITUTION: - Department of Surgery, The Methodist Hospital Research Institute, Houston, TX.

RESUMEN / SUMMARY: - The tumor microenvironment plays an important role in regulating cell growth and metastasis. Recently, we developed an ex vivo lung cancer model (four dimensional, 4D) that forms perfusable tumor nodules on a lung matrix that mimics human lung cancer histopathology and protease secretion pattern. We compared the gene expression profile (Human OneArray v5 chip) of A549 cells, a human lung cancer cell line, grown in a petri dish (two-dimensional, 2D), and of the same cells grown in the matrix of our ex vivo model (4D). Furthermore, we obtained gene expression data of A549 cells grown in a petri dish (2D) and matrigel (three-dimensional, 3D) from a previous study and compared the 3D expression profile with that of 4D. Expression array analysis showed 2,954 genes differentially expressed between 2D and 4D. Gene ontology (GO) analysis showed upregulation of several genes associated with extracellular matrix, polarity and cell fate and development. Moreover, expression array analysis of 2D vs. 3D showed 1,006 genes that were most differentially expressed, with only 36 genes (4%) having similar expression patterns as observed between 2D and 4D. Finally, the differential gene expression signature of 4D cells (vs. 2D) correlated significantly with poor survival in patients with lung cancer (n = 1,492), while the expression signature of 3D vs. 2D correlated with better survival in lung cancer patients with lung cancer. As patients with larger tumors have a worse rate of survival, the ex vivo 4D model may be a good mimic of natural progression of tumor growth in lung cancer patients.

[29]

TÍTULO / TITLE: - Volumetric tumor growth in advanced non-small cell lung cancer patients with EGFR mutations during EGFR-tyrosine kinase inhibitor therapy: Developing criteria to continue therapy beyond RECIST progression.

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

REVISTA / JOURNAL: - Cancer. 2013 Aug 6. doi: 10.1002/cncr.28290.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28290](#)

AUTORES / AUTHORS: - Nishino M; Dahlberg SE; Cardarella S; Jackman DM; Rabin MS; Ramaiya NH; Hatabu H; Janne PA; Johnson BE

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts.

RESUMEN / SUMMARY: - BACKGROUND: The objective of this study was to define the volumetric tumor growth rate in patients who had advanced nonsmall cell lung cancer (NSCLC) with sensitizing epidermal growth factor receptor (EGFR) mutations and had initially received treatment with EGFR-tyrosine kinase inhibitor (TKI) therapy beyond progression. METHODS: The study included 58 patients with advanced NSCLC who had sensitizing EGFR mutations treated with first-line gefitinib or erlotinib, had baseline computed tomography (CT) scans available that revealed a measurable lung lesion, had at least 2 follow-up CT scans during TKI therapy, and had experienced volumetric tumor growth. The tumor volume (in mm³) of the dominant lung lesion was measured on baseline and follow-up CT scans during therapy. In total, 405 volume measurements were analyzed in a linear mixed-effects model, fitting time as a random effect, to define the growth rate of the logarithm of tumor volume (log_e V). RESULTS: A linear mixed-effects model was fitted to predict the growth of log_e V, adjusting for time in months from baseline. Log_e V was estimated as a function of time in months among patients whose tumors started growing after the nadir: log_e V = 0.12*time + 7.68. In this formula, the regression coefficient for time, 0.12/month, represents the growth rate of log_e V (standard error, 0.015/month; P < .001). When adjusted for baseline volume, log_e V₀, the growth rate was also 0.12/month (standard error, 0.015/month; P < .001; log_e V = 0.12*months + 0.72 log_e V₀ + 0.61). CONCLUSIONS: Tumor volume models defined volumetric tumor growth after the nadir in patients with EGFR-mutant, advanced NSCLC who were receiving TKI, providing a reference value for the tumor growth rate in patients who progress after the nadir on TKI therapy. The results can be studied further in additional cohorts to develop practical criteria to help identify patients who are slowly progressing and can safely remain on EGFR-TKIs. Cancer 2013. © 2013 American Cancer Society.

[30]

TÍTULO / TITLE: - Prognostic impact of telomere maintenance gene polymorphisms in hepatocellular carcinoma patients with chronic Hepatitis B.

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

REVISTA / JOURNAL: - Hepatology. 2013 Aug 1. doi: 10.1002/hep.26655.

●● Enlace al texto completo (gratis o de pago) [1002/hep.26655](https://doi.org/10.1002/hep.26655)

AUTORES / AUTHORS: - Jung SW; Park NH; Shin JW; Park BR; Kim CJ; Lee JE; Shin ES; Kim JA; Chung YH

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea.

RESUMEN / SUMMARY: - Our goal was to determine whether single nucleotide polymorphisms (SNPs) of telomere maintenance genes influence the development and clinical outcomes of hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) patients. We evaluated 20 SNPs of five telomere maintenance genes in 702 patients with HCC and 351 HBsAg positive controls without HCC. Significant SNPs were then validated in an independent cohort of 857 HCCs and 429 controls. We assessed the association of each SNP with the development and overall survival by multivariate Cox proportional analysis. A significantly increased risk of HCC development was identified for TEP1 rs1713449 SNP in both the discovery and replication phases (ORcombined , 1.42; P = 9.378 x 10⁻⁵). In addition, the SNPs of TEP1 rs1713449, TEP1 rs872072, POT1 rs7784168, TERT rs13167280, and TERF1 rs2306494 had a significant effect on the overall survival and a similar survival effect was validated in the replication cohort. Moreover, there was a significant dose-dependent association between the number of putative high-risk genotypes of the above 5 SNPs regarding the overall survival. The median survival time of HCC with ≤ 2 putative high-risk genotypes was significantly prolonged compared to those with ≥ 3 high-risk genotypes (85 vs. 44 months, respectively, log-rank P = 4.483 x 10⁻⁵), which was demonstrated in the replication cohort (52 vs. 37 months, respectively, log-rank P = 0.026). Conclusion: These observations suggest that the SNPs of telomere maintenance genes play a potential role in the development and survival of HCC patients with chronic HBV infection. (Hepatology 2013;).

[31]

TÍTULO / TITLE: - An NEIL1 single nucleotide polymorphism (rs4462560) predicts the risk of radiation-induced toxicities in esophageal cancer patients treated with definitive radiotherapy.

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

REVISTA / JOURNAL: - Cancer. 2013 Sep 10. doi: 10.1002/cncr.28338.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28338](https://doi.org/10.1002/cncr.28338)

AUTORES / AUTHORS: - Chen Y; Zhu M; Zhang Z; Jiang G; Fu X; Fan M; Sun M; Wei Q; Zhao K

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - BACKGROUND: To assess the association between single nucleotide polymorphisms (SNPs) of base-excision repair genes and clinical outcomes, the roles of genetic variants of 3 selected genes-flap structure-specific endonuclease 1 (FEN1), 8-hydroxyguanine DNA glycosylase (hOGG1), and nei endonuclease VIII-like 1 (NEIL1)-were investigated in radiation-induced esophageal toxicity (RIET), radiation pneumonitis (RP), and overall survival (OS) after radio(chemo)therapy in patients with esophageal squamous cell carcinoma (ESCC). METHODS: NEIL1 reference SNP 4462560 (rs4462560) and rs7402844, hOGG1 rs1052133 and rs293795, and FEN1 rs4246215 and rs174538 were genotyped in 187 patients with ESCC who received definitive radiotherapy with or without chemotherapy. Kaplan-Meier cumulative probabilities and Cox proportional hazards regression models were used to assess the effect of the genotypes on the risk of RIET, RP, and OS. RESULTS: The authors observed that patients who had the NEIL1 rs4462560 GC/CC genotype had a statistically significantly lower risk of both grade ≥ 2 acute radiation-induced esophageal toxicity (RIET) (adjusted hazard ratio [HR], 0.421; 95% confidence interval [CI], 0.207-0.856; P = .017) and grade ≥ 2 acute radiation pneumonitis (RP) (adjusted HR, 0.392; 95% CI, 0.163-0.946; P = .037) compared with patients who had the GG genotype, but the genotype did not affect OS (adjusted HR, 0.778; 95% CI, 0.471-1.284; P = .326). There were no significant findings for other the SNPs under investigation. CONCLUSIONS: The NEIL1 rs4462560 SNP may serve as a predictor of acute RIET and RP risk but not of OS. Larger prospective studies are needed to validate these findings. Cancer 2013. © 2013 American Cancer Society.

[32]

TÍTULO / TITLE: - Comparison of the Inhibition Mechanisms of Adalimumab and Infliximab in Treating Tumor Necrosis Factor alpha-Associated Diseases from a Molecular View.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Sep 20;288(38):27059-67. doi: 10.1074/jbc.M113.491530. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.491530](#)

AUTORES / AUTHORS: - Hu S; Liang S; Guo H; Zhang D; Li H; Wang X; Yang W; Qian W; Hou S; Wang H; Guo Y; Lou Z

INSTITUCIÓN / INSTITUTION: - From the Laboratory of Structural Biology and Ministry of Education Laboratory of Protein Science, School of Medicine, Tsinghua University, Beijing 100084, China.

RESUMEN / SUMMARY: - TNFalpha-targeting therapy with the use of the drugs Etanercept, Infliximab, and Adalimumab is used in the clinical treatment of various inflammatory and immune diseases. Although all of these reagents function to disrupt the interaction between TNFalpha and its receptors, clinical investigations showed the

advantages of Adalimumab treatment compared with Etanercept and Infliximab. However, the underlying molecular mechanism of action of Adalimumab remains unclear. In our previous work, we presented structural data on how Infliximab binds with the E-F loop of TNFalpha and functions as a TNFalpha receptor-binding blocker. To further elucidate the variations between TNFalpha inhibitors, we solved the crystal structure of TNFalpha in complex with Adalimumab Fab. The structural observation and the mutagenesis analysis provided direct evidence for identifying the Adalimumab epitope on TNFalpha and revealed the mechanism of Adalimumab inhibition of TNFalpha by occupying the TNFalpha receptor-binding site. The larger antigen-antibody interface in TNFalpha Adalimumab also provided information at a molecular level for further understanding the clinical advantages of Adalimumab therapy compared with Infliximab.

[33]

TÍTULO / TITLE: - Chemotherapy-Induced Amenorrhea in Patients With Breast Cancer With a BRCA1 or BRCA2 Mutation.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 26.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2012.47.7893](#)

AUTORES / AUTHORS: - Valentini A; Finch A; Lubinski J; Byrski T; Ghadirian P; Kim-Sing C; Lynch HT; Ainsworth PJ; Neuhausen SL; Greenblatt E; Singer C; Sun P; Narod SA

INSTITUCIÓN / INSTITUTION: - Adriana Valentini, Amy Finch, Ping Sun, and Steven A. Narod, Women's College Research Institute; Ellen Greenblatt, Centre for Fertility and Reproductive Health, Mount Sinai Hospital, University of Toronto, Toronto; Peter J. Ainsworth, London Regional Cancer Program, London, Ontario; Parviz Ghadirian, Research Center of the University of Montreal Hospital Centre, Montreal, Quebec; Charmaine Kim-Sing, BC Cancer Agency, Vancouver, British Columbia, Canada; Henry T. Lynch, Creighton University School of Medicine, Omaha, NE; Susan L. Neuhausen, Beckman Research Institute, City of Hope, Duarte, CA; Jan Lubinski and Tomasz Byrski, Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland; and Christian Singer, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - PURPOSE: To determine the likelihood of long-term amenorrhea after treatment with chemotherapy in women with breast cancer who carry a BRCA1 or BRCA2 mutation. PATIENTS AND METHODS: We conducted a multicenter survey of 1,954 young women with a BRCA1 or BRCA2 mutation who were treated for breast cancer. We included premenopausal women who were diagnosed with invasive breast cancer between 26 and 47 years of age. We determined the age of onset of amenorrhea after breast cancer for women who were and were not treated with chemotherapy, alone or with tamoxifen. We considered chemotherapy-induced

amenorrhea to have occurred when the patient experienced \geq 2 years of amenorrhea, commencing within 2 years of initiating chemotherapy, with no resumption of menses. RESULTS: Of the 1,426 women who received chemotherapy, 35% experienced long-term amenorrhea. Of the 528 women who did not receive chemotherapy, 5.3% developed long-term amenorrhea. The probabilities of chemotherapy-induced amenorrhea were 7.2% for women diagnosed before age 30 years, 33% for women age 31 to 44 years, and 79% for women diagnosed after age 45 years (P trend < .001). The probability of induced amenorrhea was higher for women who received tamoxifen than for those who did not (52% v 29%; P < .001). CONCLUSION: Age at treatment and use of tamoxifen are important predictors of chemotherapy-induced amenorrhea in women who carry a BRCA1 or BRCA2 mutation. The risk of induced long-term amenorrhea does not seem to be greater among mutation carriers than among women who do not carry a mutation.

[34]

TÍTULO / TITLE: - FGF18 as a prognostic and therapeutic biomarker in ovarian cancer.

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

REVISTA / JOURNAL: - J Clin Invest. 2013 Oct 1;123(10):4435-4448. doi: 10.1172/JCI70625. Epub 2013 Sep 9.

●● Enlace al texto completo (gratis o de pago) [1172/JCI70625](#)

AUTORES / AUTHORS: - Wei W; Mok SC; Oliva E; Kim SH; Mohapatra G; Birrer MJ

RESUMEN / SUMMARY: - High-throughput genomic technologies have identified biomarkers and potential therapeutic targets for ovarian cancer. Comprehensive functional validation studies of the biological and clinical implications of these biomarkers are needed to advance them toward clinical use. Amplification of chromosomal region 5q31-5q35.3 has been used to predict poor prognosis in patients with advanced stage, high-grade serous ovarian cancer. In this study, we further dissected this large amplicon and identified the overexpression of FGF18 as an independent predictive marker for poor clinical outcome in this patient population. Using cell culture and xenograft models, we show that FGF18 signaling promoted tumor progression by modulating the ovarian tumor aggressiveness and microenvironment. FGF18 controlled migration, invasion, and tumorigenicity of ovarian cancer cells through NF- κ B activation, which increased the production of oncogenic cytokines and chemokines. This resulted in a tumor microenvironment characterized by enhanced angiogenesis and augmented tumor-associated macrophage infiltration and M2 polarization. Tumors from ovarian cancer patients had increased FGF18 expression levels with microvessel density and M2 macrophage infiltration, confirming our in vitro results. These findings demonstrate that FGF18 is important for a subset of ovarian cancers and may serve as a therapeutic target.

[35]

TÍTULO / TITLE: - Serum epidermal growth factor is associated with prognosis and hormone receptor status in patients with HER2-positive metastatic breast cancer treated with first-line trastuzumab plus taxane chemotherapy.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2268-9](#)

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

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

RESUMEN / SUMMARY: - **PURPOSE:** Epidermal growth factor (EGF) is a ligand for the epidermal growth factor receptor (EGFR). Human epidermal growth factor receptor 2 (HER2) shares common signal pathways and forms a heterodimer with EGFR. In this study, we investigated the clinical and pathologic implications of serum EGF levels in patients with HER2-positive metastatic breast cancer (MBC). **METHODS:** We analyzed serum EGF levels from baseline serum samples of consecutive patients with HER2-positive MBC who received first-line trastuzumab plus taxane chemotherapy and correlated them with treatment outcomes and pathologic features. **RESULTS:** A total of 50 women were analyzed. The median age was 47 years (range 27-72 years). Patients with high serum EGF levels (≥ 10.0 pg/mL) had significantly longer overall survival (47.0 months (95 % confidence interval (CI) 28.3-65.7 months) vs. 23.3 months (95 % CI 13.5-33.1 months); $p = 0.009$) with a tendency toward longer progression-free survival ($p = 0.123$). Serum EGF levels were not associated with hematologic or cardiac adverse events. Progesterone receptor-positive patients had significantly higher serum EGF levels than progesterone receptor-negative patients (24.3 pg/mL (range 9.5-69.0 pg/mL) vs. 12.3 pg/mL (range 0.0-59.5 pg/mL); $p = 0.006$). **CONCLUSIONS:** Our data suggest that high serum EGF levels may be associated with good prognosis in patients with HER2-positive MBC receiving trastuzumab plus taxane chemotherapy. In addition, serum EGF levels were associated with progesterone receptor positivity.

[36]

TÍTULO / TITLE: - Locally Advanced Squamous Cell Carcinoma of the Head and Neck: CT Texture and Histogram Analysis Allow Independent Prediction of Overall Survival in Patients Treated with Induction Chemotherapy.

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

REVISTA / JOURNAL: - Radiology. 2013 Aug 2.

●● Enlace al texto completo (gratis o de pago) [1148/radiol.13130110](#)

AUTORES / AUTHORS: - Zhang H; Graham CM; Elci O; Griswold ME; Zhang X; Khan MA; Pitman K; Caudell JJ; Hamilton RD; Ganeshan B; Smith AD

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Center for Biostatistics and Bioinformatics, Department of Otolaryngology, Department of Radiation Oncology, and Department of Medicine, University of Mississippi Medical Center 2500 N State St, Jackson, MS 39216; Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Fla.

RESUMEN / SUMMARY: - Purpose: To determine if computed tomographic (CT) texture and histogram analysis measurements of the primary mass are independently associated with overall survival in patients with locally advanced squamous cell carcinoma of the head and neck who were previously treated with cisplatin, 5-fluorouracil, and docetaxel (TPF) induction chemotherapy. Materials and Methods: This institutional review board-approved retrospective study included 72 patients with locally advanced squamous cell carcinoma of the head and neck who were treated with induction TPF chemotherapy in 2004-2010. CT texture and histogram analysis of the primary mass on the pretherapy CT images were performed by using TexRAD software before and after application of spatial filters at different anatomic scales ranging from fine detail to coarse features. Cox proportional hazards models were used to examine the association between overall survival and the baseline CT imaging measurements and clinical variables. Results: Primary mass entropy and skewness measurements with multiple spatial filters were associated with overall survival. Multivariate Cox regression analysis incorporating clinical and imaging variables indicated that primary mass size (hazard ratio [HR], 1.58 for each 1-cm increase; P = .018), N stage (HR, 8.77 for N3 vs N0 or N1; P = .002; HR, 4.99 for N3 vs N2; P = .001), and primary mass entropy (HR, 2.10 for each 0.5-unit increase; P = .036) and skewness (HR, 3.67 for each 1.0-unit increase; P = .009) measurements with the 1.0 spatial filter were independently associated with overall survival. Conclusion: Independent of tumor size, N stage, and other clinical variables, primary mass CT texture and histogram analysis parameters are associated with overall survival in patients with locally advanced squamous cell carcinoma of the head and neck who were treated with induction TPF. © RSNA, 2013

Supplemental material:

<http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13130110/-/DC1>.

[37]

TÍTULO / TITLE: - Metastatic Melanoma: Lactate Dehydrogenase Levels and CT Imaging Findings of Tumor Devascularization Allow Accurate Prediction of Survival in Patients Treated with Bevacizumab.

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

REVISTA / JOURNAL: - Radiology. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1148/radiol.13130776](http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13130776)

AUTORES / AUTHORS: - Gray MR; Martin Del Campo S; Zhang X; Zhang H; Souza FF; Carson WE 3rd; Smith AD

INSTITUCIÓN / INSTITUTION: - Department of Radiology, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216.

RESUMEN / SUMMARY: - Purpose: To predict survival in patients with metastatic melanoma by evaluating a combination of serum lactate dehydrogenase (LDH) level and initial computed tomographic (CT) findings of tumor devascularization after antiangiogenic therapy. Materials and Methods: Consent was waived for this institutional review board-approved, retrospective, secondary analysis. Forty-four patients with metastatic melanoma received bevacizumab therapy in a randomized prospective phase II trial. Target lesions on the initial posttherapy CT images were evaluated by using Response Evaluation Criteria in Solid Tumors, the Choi criteria, and Morphology, Attenuation, Size, and Structure (MASS) criteria. Cox proportional hazards models were used to assess the association of baseline clinical variables including serum LDH and imaging findings with progression-free and overall survival. The receiver operating characteristic curve with area under the curve (AUC) was used to evaluate accuracy. Results: In multivariate analysis, a high baseline serum LDH level was associated with decreased progression-free survival (hazard ratio = 1.29 for each increase of 100 IU/L; $P = .002$) and overall survival (hazard ratio = 1.44 for each increase of 100 IU/L; $P = .001$). Evaluation with MASS criteria of the first CT examination after therapy strongly predicted progression-free ($P < .001$) and overall ($P < .001$) survival. Baseline serum LDH level was moderately accurate for predicting progression-free survival at 9 months (AUC = 0.793) and overall survival at 18 months (AUC = 0.689). The combination of baseline serum LDH levels and evaluation with MASS criteria at the first CT examination after therapy had significantly higher accuracy for predicting progression-free survival at 9 months (AUC = 0.969) and overall survival at 18 months (AUC = 0.813) than did baseline serum LDH levels alone for prediction of progression-free survival ($P = .020$). Conclusion: A combination of baseline serum LDH levels and evaluation with MASS criteria at the first CT examination after bevacizumab therapy had the highest accuracy for predicting survival in patients with metastatic melanoma. © RSNA, 2013 Supplemental material:

<http://radiology.rsna.org/lookup/suppl/doi:10.1148/radiol.13130776/-/DC1>.

[38]

TÍTULO / TITLE: - IFNL4 rs469415590 variant is a better predictor than ILF3 (IL28B) rs12979860 of pegylated interferon-alpha/ribavirin therapy failure in hepatitis C virus/HIV-1 coinfecting patients.

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

REVISTA / JOURNAL: - AIDS. 2013 Sep 25.

- Enlace al texto completo (gratis o de pago)

[1097/QAD.0000000000000052](https://doi.org/10.1097/QAD.0000000000000052)

AUTORES / AUTHORS: - Franco S; Aparicio E; Parera M; Clotet B; Tural C; Martinez MA

INSTITUCIÓN / INSTITUTION: - aFundacio irsiCaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona (UAB), Badalona bFundacio de la Lluita contra la Sida, Hospital Universitari Germans Trias i Pujol, Badalona, España.

RESUMEN / SUMMARY: - A new transiently induced region (IFNL4) harbouring a dinucleotide variant ss469415590 (TT or DeltaG), upstream of IFNL3 (IL28B), was recently found to be associated with hepatitis C virus (HCV) clearance. To determine the effect of IFNL4 ss469415590 variation on the HCV response to IFN-based therapy in HCV/HIV-1 coinfecting patients, ss469415590 was genotyped in a cohort of 207 patients from our clinic. Treatment failure occurred in 77% of minor DeltaG-allele carriers versus 48% of noncarriers, indicating that the DeltaG allele was strongly associated with treatment failure. Importantly, multivariate logistic analysis revealed that ss469415590 genotype was a better predictor of treatment failure than IFNL3 rs12979860.

[39]

TÍTULO / TITLE: - XPF protein levels determine sensitivity of malignant melanoma cells to oxaliplatin chemotherapy: Suitability as a biomarker for patient selection.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 26. doi: 10.1002/ijc.28454.

- Enlace al texto completo (gratis o de pago) [1002/ijc.28454](https://doi.org/10.1002/ijc.28454)

AUTORES / AUTHORS: - Hatch SB; Swift LP; Caporali S; Carter R; Hill EJ; Macgregor TP; D'Atri S; Middleton MR; McHugh PJ; Sharma RA

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Oxford NIHR Biomedical Research Centre, Cancer Research UK-Medical Research Council Gray Institute for Radiation Oncology & Biology, Old Road Campus Research Building, University of Oxford, Oxford, OX3 7DQ, UK.

RESUMEN / SUMMARY: - As the options for systemic treatment of malignant melanoma (MM) increase, the need to develop biomarkers to identify patients who might benefit from cytotoxic chemotherapy becomes more apparent. In preclinical models, oxaliplatin has activity in cisplatin-resistant cells. In this study, we have shown that oxaliplatin forms inter-strand cross-links (ICLs) in cellular DNA and that loss of the heterodimeric structure-specific endonuclease XPF-ERCC1 causes hypersensitivity to oxaliplatin in mammalian cells. XPF deficiency resulted in late S-phase arrest and persistence of double-strand breaks following oxaliplatin treatment. In a panel of 12 MM cell lines, oxaliplatin sensitivity correlated with XPF and ERCC1 protein levels. Knockdown of ERCC1 and XPF protein levels by RNA interference increased sensitivity of cancer cells to oxaliplatin; overexpression of exogenous ERCC1 significantly

decreased drug sensitivity. Following immunohistochemical optimisation, XPF protein levels were quantified in MM tissue samples from 183 patients, showing variation in expression and no correlation with prognosis. In 57 patients with MM treated with cisplatin or carboplatin, XPF protein levels did not predict the likelihood of clinical response. We propose that oxaliplatin should not be discarded as a potential treatment for MM on the basis of the limited activity of cisplatin in unselected patients. Moreover, we show that XPF-ERCC1 protein levels are a key determinant of the sensitivity of melanoma cells to oxaliplatin in vitro. Immunohistochemical detection of XPF appears suitable for development as a tissue biomarker for potentially selecting patients for oxaliplatin treatment in a prospective clinical trial. © 2013 Wiley Periodicals, Inc.

[40]

TÍTULO / TITLE: - Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer.

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

REVISTA / JOURNAL: - J Clin Invest. 2013 Aug 1;123(8):3190-200. doi: 10.1172/JCI70212. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1172/JCI70212](#)

AUTORES / AUTHORS: - Welti J; Loges S; Dimmeler S; Carmeliet P

INSTITUCIÓN / INSTITUTION: - Vesalius Research Center, University of Leuven, Leuven, Belgium.

RESUMEN / SUMMARY: - Four decades ago, angiogenesis was recognized as a therapeutic target for blocking cancer growth. Because of its importance, VEGF has been at the center stage of antiangiogenic therapy. Now, several years after FDA approval of an anti-VEGF antibody as the first antiangiogenic agent, many patients with cancer and ocular neovascularization have benefited from VEGF-targeted therapy; however, this anticancer strategy is challenged by insufficient efficacy, intrinsic refractoriness, and resistance. Here, we examine recent discoveries of new mechanisms underlying angiogenesis, discuss successes and challenges of current antiangiogenic therapy, and highlight emerging antiangiogenic paradigms.

[41]

TÍTULO / TITLE: - The Bcl-2 homology 3 (BH3)-only proteins Bim and Bid are functionally active and restrained by anti-apoptotic B-cell CLL/lymphoma 2 (Bcl-2) family proteins in healthy liver.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M112.443093](#)

AUTORES / AUTHORS: - Kodama T; Hikita H; Kawaguchi T; Saito Y; Tanaka S; Shigekawa M; Shimizu S; Li W; Miyagi T; Kanto T; Hiramatsu N; Tatsumi T; Takehara T

INSTITUCIÓN / INSTITUTION: - Osaka University Graduate School of Medicine, Japan.

RESUMEN / SUMMARY: - Background and Aim: An intrinsic pathway of apoptosis is regulated by the B-cell lymphoma-2 (Bcl-2) family proteins. We previously reported that a fine rheostatic balance between the anti- and pro-apoptotic multi-domain Bcl-2 family proteins controls hepatocyte apoptosis in the healthy liver. The Bcl-2 homology domain 3 (BH3)-only proteins set this rheostatic balance toward apoptosis upon activation in the diseased liver. However, their involvement in healthy Bcl-2 rheostasis remains unknown. In the present study, we focused on two BH3-only proteins, Bim and Bid, and we clarified the Bcl-2 network that governs hepatocyte life and death in the healthy liver. Methods: We generated hepatocyte-specific Bcl-xL- or Mcl-1-knockout mice, with or without disrupting Bim and/or Bid, and we examined hepatocyte apoptosis under physiological conditions. We also examined the effect of both Bid and Bim disruption on the hepatocyte apoptosis caused by the inhibition of Bcl-xL and Mcl-1. Results: Spontaneous hepatocyte apoptosis in Bcl-xL- or Mcl-1-knockout mice was significantly ameliorated by Bim deletion. The disruption of both Bim and Bid completely prevented hepatocyte apoptosis in Bcl-xL-knockout mice and weakened massive hepatocyte apoptosis via the additional in vivo knockdown of mcl-1 in these mice. Finally, the hepatocyte apoptosis caused by ABT-737, which is a Bcl-xL/Bcl-2/Bcl-w inhibitor, was completely prevented in Bim/Bid double knockout mice. Conclusion: The BH3-only proteins Bim and Bid are functionally active but are restrained by the anti-apoptotic Bcl-2 family proteins under physiological conditions. Hepatocyte integrity is maintained by the dynamic and well-orchestrated Bcl-2 network in the healthy liver.

TÍTULO / TITLE: - Markers of angiogenesis (CD31, CD34, rCBV) and their prognostic value in low-grade gliomas.

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

REVISTA / JOURNAL: - Neurol Neurochir Pol. 2013 Jul-Aug;47(4):325-31.

AUTORES / AUTHORS: - Majchrzak K; Kaspera W; Szymas J; Bobek-Billewicz B; Hebda A; Majchrzak H

INSTITUCIÓN / INSTITUTION: - Katedra i Oddział Kliniczny Neurochirurgii, Sosnowiec.
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RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Antigens CD31 and CD34 and relative cerebral blood volume (rCBV) in gliomas reflect in different ways neoangiogenesis of the tumour. Thus, we decided: (1) to estimate the correlation between the values of CD31 and CD34 and the value of rCBV in low-grade gliomas (LGG), and (2) to establish the prognostic value of these markers. MATERIAL AND METHODS: The investigated group consisted of 53 patients with LGG who were

operated on in the Neurosurgical Department at Sosnowiec between 2005 and 2011. On the basis of perfusion-weighted imaging (PWI-MRI) in the tumour texture, rCBV was calculated. The values of CD31 and CD34 were estimated on the basis of immunohistochemical investigation. Three outcome measures were assessed: (1) overall survival, (2) progression-free survival, and (3) malignant-free survival. Statistical analyses were done using the STATISTICA 9.0 program. RESULTS: Higher value of rCBV in the texture of LGG significantly correlated with higher CD31 ($p = 0.0006$) and CD34 values ($p = 0.0043$). Progression-free survival was significantly longer in patients with $rCBV < 1.75$ than for persons with $rCBV > 1.75$ ($p = 0.015$). Lower expression of CD31 correlated with probability of longer survival of the patients after the operation of LGG ($p = 0.068$). CONCLUSIONS: Density of microvessels as assessed immunohistochemically with CD31+ and CD34+ in LGG correlated with the value of rCBV in the tumour. The value of 1.75 for rCBV may be the threshold for better or poorer outcome of these patients. Expression of CD31 antigen is an important prognostic factor for the time of survival for patients with LGG.

[42]

TÍTULO / TITLE: - S-1 plus irinotecan and oxaliplatin for the first-line treatment of patients with metastatic colorectal cancer: a prospective phase II study and pharmacogenetic analysis.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17;109(6):1420-7. doi: 10.1038/bjc.2013.479. Epub 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.479](#)

AUTORES / AUTHORS: - Kim SY; S Hong Y; K Shim E; Kong SY; Shin A; Baek JY; Jung KH

INSTITUCIÓN / INSTITUTION: - Center for Colorectal Cancer, Research Institute and Hospital, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 410-769, Korea.

RESUMEN / SUMMARY: - Background:S-1 is an oral fluoropyrimidine that mimics infusional 5-fluorouracil. The aim of this phase II trial was to explore the clinical efficacy of the triplet regimen TIROX, which consists of S-1, irinotecan and oxaliplatin. Methods:Forty-two chemo-naive patients with metastatic colorectal cancer (mCRC) were planned to be enrolled and be treated with irinotecan 150 mg m^{-2} followed by oxaliplatin 85 mg m^{-2} on day 1 and S-1 80 mg m^{-2} per day from day 1 to 14 every 3 weeks. Polymorphisms in the UGT1A1, UGT1A6, UGT1A7 and CYP2A6 genes were analysed. Results:Between July 2007 and February 2008, 43 patients were enrolled. An objective response was noted in 29 patients (67.4%, 95% confidence interval: 53.4-81.4), of which 2 achieved durable complete responses. The median progression-free survival was 10.0 months and the median overall survival was 19.2 months. Significant grade 3 or 4 adverse events were neutropenia (45.2%), febrile neutropenia (9.5%), diarrhoea (7.1%) and vomiting (9.5%). Increased gastrointestinal

toxicities were associated with the presence of UGT1A6*2 or UGT1A7*3 and an improved tumour response was noted in those without variant alleles of CYP2A6 or UGT1A1*60. Conclusion: The combination of S-1, irinotecan and oxaliplatin showed favourable efficacy and tolerability in untreated patients with mCRC.

[43]

TÍTULO / TITLE: - A transcriptional and metabolic signature of primary aneuploidy is present in chromosomally-unstable cancer cells and informs clinical prognosis.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0749](#)

AUTORES / AUTHORS: - Sheltzer JM

INSTITUCIÓN / INSTITUTION: - Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology.

RESUMEN / SUMMARY: - Aneuploidy is invariably associated with poor proliferation of primary cells, but the precise contributions of abnormal karyotypes to cancer, a disease characterized by aneuploidy and dysregulated proliferation, remain unclear. In this study, I demonstrate that the transcriptional alterations caused by aneuploidy in primary cells are also present in chromosomally-unstable cancer cell lines, but the same alterations are not common to all aneuploid cancers. Chromosomally-unstable cancer lines displayed increased glycolytic and TCA-cycle flux, also a feature of aneuploid primary cells. The biological response to aneuploidy is associated with cellular stress and slow proliferation, and a 70-gene signature derived from primary aneuploid cells was defined as a strong predictor of increased survival in several cancers. Inversely, a transcriptional signature derived from clonal aneuploidy in tumors correlated with high mitotic activity and poor prognosis. Together these findings suggested that there are two types of aneuploidy in cancer, one of which is clonal aneuploidy selected during tumor evolution and associated with robust growth, and the second of which is subclonal aneuploidy caused by chromosomal instability (CIN). Subclonal aneuploidy more closely resembles the stressed state of primary aneuploid cells, yet CIN is not benign: a subset of genes upregulated in high-CIN cancers predict aggressive disease in human patients in a proliferation-independent manner.

[44]

TÍTULO / TITLE: - Erythropoietin activates cell survival pathways in breast cancer stem-like cells to protect them from chemotherapy.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-0248](https://doi.org/10.1158/0008-5472.CAN-13-0248)

AUTORES / AUTHORS: - Todaro M; Turdo A; Bartucci M; Iovino F; Dattilo R; Biffoni M; Stassi G; Federici G; De Maria R; Zeuner A

INSTITUCIÓN / INSTITUTION: - Department of Surgical and Oncological Sciences, University of Palermo.

RESUMEN / SUMMARY: - Recombinant erythropoietin (EPO) analogs (ESAs, erythropoiesis-stimulating agents) are clinically used to treat anemia in cancer patients receiving chemotherapy. After clinical trials reporting increased adverse events and/or reduced survival in ESAs-treated patients, concerns have raised about the potential role of ESAs in promoting tumor progression, possibly through tumor cell stimulation. However, evidence is lacking on the ability of EPO to directly affect cancer stem-like cells, which are thought to be responsible for tumor progression and relapse. We found that breast cancer stem-like cells (BCSC) isolated from patient tumors express the EPO receptor and respond to EPO treatment with increased proliferation and self-renewal. Importantly, EPO stimulation increased BCSC resistance to chemotherapeutic agents and activated cellular pathways responsible for survival and drug resistance. Specifically, the Akt and ERK pathways were activated in BCSC at early time points following EPO treatment, while Bcl-xL levels increased at later times. In vivo, EPO administration counteracted the effects of chemotherapeutic agents on BCSC-derived orthotopic tumor xenografts and promoted metastatic progression both in the presence and in the absence of chemotherapy treatment. Altogether, these results indicate that Epo acts directly on BCSC by activating specific survival pathways, resulting in BCSC protection from chemotherapy and enhanced tumor progression.

[45]

- CASTELLANO -

TÍTULO / TITLE: Valeur pejorative des variations de poids en cours de chimiothérapie dans le cancer du sein non métastatique : causes, mécanismes impliqués et stratégies préventives.

TÍTULO / TITLE: - Poor prognostic value of weight change during chemotherapy in non-metastatic breast cancer patients: causes, mechanisms involved and preventive strategies.

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

REVISTA / JOURNAL: - Bull Cancer. 2013 Sep 1;100(9):865-870.

●● Enlace al texto completo (gratis o de pago) [1684/bdc.2013.1802](https://doi.org/10.1684/bdc.2013.1802)

AUTORES / AUTHORS: - Gadea E; Thivat E; Wang-Lopez Q; Viala M; Paulon R; Planchat E; Chadeyras JB; Merlin C; Coudert B; Bignon YJ; Morio B; Durando X

INSTITUCIÓN / INSTITUTION: - Centre Jean-Perrin, 58, rue Montalembert, BP 392, 63011 Clermont-Ferrand cedex 1, France, Inra/UdA, UMR 1019 Human Nutrition, CHLEO,

63000 Clermont-Ferrand, France, Centre d'investigation clinique, 63000 Clermont-Ferrand, France.

RESUMEN / SUMMARY: - Numerous studies have demonstrated that a significant change in weight during chemotherapy treatment was a factor of poor prognosis in early breast cancer women. However, the causes and mechanisms involved in this phenomenon are not fully known. This review summarizes current knowledge about the causes of energy imbalance during chemotherapy treatment and the mechanisms that have been proposed as responsible for the increased risk of relapse and death in this population. Current preventive strategies focus on physical activity programs but also on the use of metformin during and after chemotherapy.

[46]

TÍTULO / TITLE: - Predicting time to ovarian carcinoma recurrence using protein markers.

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

REVISTA / JOURNAL: - J Clin Invest. 2013 Sep 3;123(9):3740-50. doi: 10.1172/JCI68509. Epub 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1172/JCI68509](#)

AUTORES / AUTHORS: - Yang JY; Yoshihara K; Tanaka K; Hatae M; Masuzaki H; Itamochi H; Takano M; Ushijima K; Tanyi JL; Coukos G; Lu Y; Mills GB; Verhaak RG

RESUMEN / SUMMARY: - Patients with ovarian cancer are at high risk of tumor recurrence. Prediction of therapy outcome may provide therapeutic avenues to improve patient outcomes. Using reverse-phase protein arrays, we generated ovarian carcinoma protein expression profiles on 412 cases from TCGA and constructed a Protein-driven index of OVARian cancer (PROVAR). PROVAR significantly discriminated an independent cohort of 226 high-grade serous ovarian carcinomas into groups of high risk and low risk of tumor recurrence as well as short-term and long-term survivors. Comparison with gene expression-based outcome classification models showed a significantly improved capacity of the protein-based PROVAR to predict tumor progression. Identification of protein markers linked to disease recurrence may yield insights into tumor biology. When combined with features known to be associated with outcome, such as BRCA mutation, PROVAR may provide clinically useful predictions of time to tumor recurrence.

[47]

TÍTULO / TITLE: - Ethinylestradiol is beneficial for postmenopausal patients with heavily pre-treated metastatic breast cancer after prior aromatase inhibitor treatment: a prospective study.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17;109(6):1537-42. doi: 10.1038/bjc.2013.520. Epub 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.520](https://doi.org/10.1038/bjc.2013.520)

AUTORES / AUTHORS: - Iwase H; Yamamoto Y; Yamamoto-Ibusuki M; Murakami KI; Okumura Y; Tomita S; Inao T; Honda Y; Omoto Y; Iyama KI

INSTITUCIÓN / INSTITUTION: - Department of Breast and Endocrine Surgery, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.

RESUMEN / SUMMARY: - Background: Oestrogens usually stimulate the progression of oestrogen receptor (ER)-positive breast cancer. Paradoxically, high-dose oestrogens suppress the growth of these tumours in certain circumstances. Methods: We prospectively examined the efficacy and safety of ethinylestradiol treatment (3 mg per day oral) in postmenopausal patients with advanced or recurrent ER-positive breast cancer who had previously received endocrine therapies, especially those with resistance to aromatase inhibitors. Results: Eighteen patients were enrolled with the median age of 63 years and the mean observation time of 9.2 months. Three cases withdrew within 1 week due to oestrogen flare reactions with nausea, fatigue and muscle-skeletal pain. The response rate was 50% (9 out of 18), and the clinical benefit rate was 56% (10 out of 18). The stable disease (<6 months) was 17% (3 out of 18) and another 2 cases were judged as progressive disease. Time-to-treatment failure including 2 on treatment was a median of 5.6 months (range 0.1 to 14.5(+)). Although vaginal bleeding or endometrial thickening was observed in patients receiving long-term treatment, there were no severe adverse events, such as deep venous thrombosis or other malignancies. Conclusion: Although the mechanism of this treatment has not been fully understood, our data may contribute to change the common view of late-stage endocrine therapy.

[48]

TÍTULO / TITLE: - Seven-year follow-up of allogeneic transplant using BCNU, etoposide, cytarabine and melphalan chemotherapy in patients with Hodgkin lymphoma after autograft failure: importance of minimal residual disease.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Oct 3.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.838233](https://doi.org/10.3109/10428194.2013.838233)

AUTORES / AUTHORS: - Sobol U; Rodriguez T; Smith S; Go A; Vimr R; Parthasarathy M; Guo R; Stiff P

INSTITUCIÓN / INSTITUTION: - Loyola University Medical Center, Maywood, IL, USA.

RESUMEN / SUMMARY: - Allogeneic transplant using reduced intensity conditioning is a therapeutic option for patients with Hodgkin lymphoma (HL) who relapse after an autograft. This was a prospective study of 31 consecutive eligible patients with HL who relapsed after an autograft and underwent an allograft using BEAM (BCNU, etoposide,

cytarabine, melphalan) conditioning. At a median follow-up of 7 years the progression-free survival (PFS) was 36% (95% confidence interval [CI] 19-54%) and overall survival (OS) was 42% (95% CI 23-59%). In multivariate analysis only residual disease at the time of transplant predicted outcome, with a 4-year PFS and OS of 62% and 75% for patients with minimal residual disease versus 8% and 8% for patients with gross residual disease, respectively ($p = 0.005$ and $p = 0.001$, respectively). This benefit seemed to be irrespective of chemosensitivity, with an OS for patients with chemorefractory yet minimal disease of 71% at 4 years. BEAM allogeneic transplant is effective in producing long-term remissions after autograft failure. Regardless of chemosensitivity, minimizing tumor burden pre-transplant may improve long-term outcome.

[49]

TÍTULO / TITLE: - Integrating in vitro sensitivity and dose-response slope is predictive of clinical response to ABL kinase inhibitors in chronic myeloid leukemia.

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

REVISTA / JOURNAL: - Blood. 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2012-08-452409](https://doi.org/10.1182/blood-2012-08-452409)

AUTORES / AUTHORS: - Vainstein V; Eide CA; O'Hare T; Shukron O; Druker BJ

INSTITUCIÓN / INSTITUTION: - Division of Hematology, Hadassah Medical Center, Jerusalem, Israel;

RESUMEN / SUMMARY: - BCR-ABL mutations result in clinical resistance to ABL tyrosine kinase inhibitors (TKIs) in CML. Although in vitro IC50 values for specific mutations have been suggested to guide TKI choice in the clinic, quantitative relationship between IC50 and clinical response has never been demonstrated. We used Hill's equation for in vitro response of Ba/F3 cells transduced with various BCR-ABL mutants to determine IC50 and the slope of the dose-response curve. We found that slope variability between mutants tracked with in vitro TKI resistance, providing particular additional interpretive value in cases where in vitro IC50 and clinical response are disparate. Moreover, unlike IC50 alone, higher inhibitory potential at peak concentration (IPP), which integrates IC50, slope, and Cmax, correlated with improved complete cytogenetic response (CCyR) rates in CML patients treated with dasatinib. Our findings suggest a metric integrating in vitro and clinical data may provide an improved tool for BCR-ABL mutation-guided TKI selection.

[50]

TÍTULO / TITLE: - Incidence and relative risk of hepatic toxicity in patients treated with antiangiogenic tyrosine kinase inhibitors for malignancy.

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

REVISTA / JOURNAL: - Br J Clin Pharmacol. 2013 Aug 28. doi: 10.1111/bcp.12231.

●● Enlace al texto completo (gratis o de pago) [1111/bcp.12231](https://doi.org/10.1111/bcp.12231)

AUTORES / AUTHORS: - Iacovelli R; Palazzo A; Procopio G; Santoni M; Trenta P; de Benedetto A; Mezi S; Cortesi E

INSTITUCIÓN / INSTITUTION: - Sapienza University of Rome, Department of Radiology, Oncology and Human Pathology, Oncology Unit B; Rome, Italy; Viale Regina Elena 324 - 00161 Rome, Italy.

RESUMEN / SUMMARY: - AIM: The aim of this study is to investigate the incidence and risk of hepatic toxicity in patients receiving TKIs through a large up-to-date meta-analysis of available clinical trials. METHODS: PubMed was reviewed for phase III randomized trials with axitinib, pazopanib, sorafenib, sunitinib, regorafenib or vandetanib. The characteristics of each study and incidence of all- and high-grades of ALT, AST and total bilirubin increase were collected. RESULTS: A total of 3,691 patients was available for meta-analysis: 1,170 had metastatic renal cell carcinoma; 950 had advanced non-small cell lung carcinoma; 454 had hepatocarcinoma; 753 had metastatic colorectal cancer, and 362 had metastatic soft-tissue sarcoma. The incidence of ALT, AST and bilirubin increase of any grade in patients treated with TKIs was 34.0% (95% CI, 31.6 - 36.3), 39.2% (95% CI, 36.7 - 41.6), and 21.8% (95% CI, 19.9 - 23.7), respectively. The incidence of the high-grade increase was 5.2% (95% CI, 4.2 - 6.4), 5.0% (95% CI, 3.8 - 6.2) and 1.7% (95% CI, 1.1 - 2.4) respectively. The relative risk of ALT, AST and total bilirubin increase resulted 1.85, 2.19 and 1.79 for any grade and 2.75, 2.39 and 1.65 for high grade, respectively. CONCLUSIONS: Hepatotoxicity is a relative common event occurring in 23-40% of patients treated with TKIs. Despite this, only 5% of patients have had high grade of toxicity. A better knowledge of this phenomenon may prevent high-grade toxicity and reduce treatment discontinuation due to this adverse event.

[51]

TÍTULO / TITLE: - Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: Correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials.

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

REVISTA / JOURNAL: - Radiother Oncol. 2013 Sep 20. pii: S0167-8140(13)00436-2. doi: 10.1016/j.radonc.2013.08.036.

●● Enlace al texto completo (gratis o de pago) [1016/j.radonc.2013.08.036](https://doi.org/10.1016/j.radonc.2013.08.036)

AUTORES / AUTHORS: - Lassen P; Overgaard J; Eriksen JG

INSTITUCIÓN / INSTITUTION: - Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark.

RESUMEN / SUMMARY: - AIM: EGFR and HPV-associated p16 are among the most investigated biomarkers in head and neck cancer. The aim was to investigate the

correlation and interaction between these two markers and to evaluate their potential prognostic significance when combined. MATERIALS AND METHODS: 336 Oropharyngeal carcinomas treated with primary radiotherapy (66-68Gy, 2fx/day, 10-12Gy/week) and with known EGFR/p16-status estimated semiquantitatively by immunohistochemistry were included in the study. Data were evaluated by EGFR-expression (high/low) and p16-status (positive/negative) consequently dividing tumours into four groups by combination of the biomarkers. Patient/tumour characteristics and complete 5-year follow-up were available. RESULTS: Low EGFR-expression was significantly more common in p16-positive tumours compared to p16-negative, $p < 0.0001$. p16 positivity showed a strong prognostic impact ($p < 0.0001$, $HR = 0.22 [0.13-0.38]$), whereas EGFR was a weak prognostic marker when local control was used as endpoint ($p = 0.03$, $HR = 0.53 [0.29-0.94]$). Combination of EGFR/p16 did not add significant information to p16 alone and by multivariable analysis only p16 showed significant prognostic information for all evaluated endpoints. CONCLUSIONS: Both EGFR and p16 bear prognostic information in oropharyngeal cancer, although p16 is, by far, the strongest prognostic factor. The markers seem to be correlated and this might have influence when evaluating the effect of EGFR inhibition in oropharyngeal tumours.

[52]

TÍTULO / TITLE: - Re: Selective Inhibition of Her2-Positive Breast Cancer Cells by the HIV Protease Inhibitor Nelfinavir.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Oct 2;105(19):1515. Epub 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt238](#)

AUTORES / AUTHORS: - Kapoor S

[53]

TÍTULO / TITLE: - Montreal prognostic score: estimating survival of patients with non-small cell lung cancer using clinical biomarkers.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 24. doi: 10.1038/bjc.2013.515.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.515](#)

AUTORES / AUTHORS: - Gagnon B; Agulnik JS; Gioulbasanis I; Kasymjanova G; Morris D; Macdonald N

INSTITUCIÓN / INSTITUTION: - Department of Family Medicine and Emergency Medicine, Université Laval, Centre de Recherche du Le Centre Hospitalier Universitaire de Québec, 9 rue McMahon, Local 1899-6, Québec, Québec City, Québec QC G1R 2J6, Canada.

RESUMEN / SUMMARY: - Background: For evidence-based medical practice, well-defined risk scoring systems are essential to identify patients with a poor prognosis. The objective of this study was to develop a prognostic score, the Montreal prognostic score (MPS), to improve prognostication of patients with incurable non-small cell lung cancer (NSCLC) in everyday practice. Methods: A training cohort (TC) and a confirmatory cohort (CC) of newly diagnosed patients with NSCLC planning to receive chemotherapy were used to develop the MPS. Stage and clinically available biomarkers were entered into a Cox model and risk weights were estimated. C-statistics were used to test the accuracy. Results: The TC consisted of 258 patients and the CC consisted of 433 patients. Montreal prognostic score classified patients into three distinct groups with median survivals of 2.5 months (95% confidence interval (CI): 1.8, 4.2), 8.2 months (95% CI: 7.0, 9.4) and 18.2 months (95% CI: 14.0, 27.5), respectively (log-rank, $P < 0.001$). Overall, the C-statistics were 0.691 (95% CI: 0.685, 0.697) for the TC and 0.665 (95% CI: 0.661, 0.670) for the CC. Conclusion: The MPS, by classifying patients into three well-defined prognostic groups, provides valuable information, which physicians could use to better inform their patients about treatment options, especially the best timing to involve palliative care teams. British Journal of Cancer advance online publication, 24 September 2013; doi:10.1038/bjc.2013.515 www.bjcancer.com.

[54]

TÍTULO / TITLE: - Prognostic Value of Mucinous Histology Depends on Microsatellite Instability Status in Patients with Stage III Colon Cancer Treated with Adjuvant FOLFOX Chemotherapy: A Retrospective Cohort Study.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Oct;20(11):3407-13. doi: 10.1245/s10434-013-3169-1. Epub 2013 Aug 14.

●● Enlace al texto completo (gratuito o de pago) [1245/s10434-013-3169-1](#)

AUTORES / AUTHORS: - Kim SH; Shin SJ; Lee KY; Kim H; Kim TI; Kang DR; Hur H; Min BS; Kim NK; Chung HC; Roh JK; Ahn JB

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND: The close association between mucinous histology and microsatellite instability (MSI) may have hindered the evaluation of prognostic significance of mucinous histology. The aim of this retrospective study was to investigate whether mucinous histology was associated with a worse prognosis, independent of MSI status, compared to nonmucinous histology in patients with stage III colon cancer. METHODS: This study enrolled 394 consecutive patients with stage III colorectal cancer treated with adjuvant FOLFOX after curative resection (R0). Clinicopathological information was retrospectively reviewed. Tumors were analyzed

for MSI by polymerase chain reaction to determine MSI status. Kaplan-Meier method, log-rank test, and Cox proportional hazard regression models were used. RESULTS: The estimated rate of 3-year disease-free survival (DFS) in patients with nonmucinous adenocarcinoma (NMA 79.2 %) was significantly greater than that in patients with mucinous adenocarcinoma (MA) and adenocarcinoma with mucinous component (MC) (56.9 %; log-rank, P = 0.002). In univariate analysis, histology (NMA vs. MA/MC), American Joint Committee on Cancer stage (IIIA, IIIB, and IIIC), and lymphovascular invasion (present vs. absent) were significantly associated with DFS. In multivariate analysis, mucinous histology (MA/MC) was associated with decreased DFS in all patients (hazard ratio 1.82, 95 % confidence interval 1.03-3.23, P = 0.0403). In patients with MA/MC, no difference in DFS was observed between MSI and microsatellite stability (log-rank, P = 0.732). CONCLUSIONS: Mucinous histology is an independent poor prognostic factor for DFS in patients with stage III colon cancer after adjuvant FOLFOX chemotherapy.

[55]

TÍTULO / TITLE: - NUP98-NSD1 fusion in association with FLT3-ITD mutation identifies a prognostically relevant subgroup of pediatric acute myeloid leukemia patients suitable for monitoring by real time quantitative PCR.

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

REVISTA / JOURNAL: - Genes Chromosomes Cancer. 2013 Nov;52(11):1053-64. doi: 10.1002/gcc.22100. Epub 2013 Sep 2.

●● Enlace al texto completo (gratis o de pago) [1002/gcc.22100](#)

AUTORES / AUTHORS: - Akiki S; Dyer SA; Grimwade D; Ivey A; Abou-Zeid N; Borrow J; Jeffries S; Caddick J; Newell H; Begum S; Tawana K; Mason J; Velangi M; Griffiths M

INSTITUCIÓN / INSTITUTION: - West Midlands Regional Genetics Laboratory, Birmingham Women's NHS foundation Trust, Birmingham, UK; School of Cancer Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.

RESUMEN / SUMMARY: - The cytogenetically cryptic t(5;11)(q35;p15) leading to the NUP98-NSD1 fusion is a rare but recurrent gene rearrangement recently reported to identify a group of young AML patients with poor prognosis. We used reverse transcription polymerase chain reaction (PCR) to screen retrospectively diagnostic samples from 54 unselected pediatric AML patients and designed a real time quantitative PCR assay to track individual patient response to treatment. Four positive cases (7%) were identified; three arising de novo and one therapy related AML. All had intermediate risk cytogenetic markers and a concurrent FLT3-ITD but lacked NPM1 and CEBPA mutations. The patients had a poor response to therapy and all proceeded to hematopoietic stem cell transplant. These data lend support to the adoption of screening for NUP98-NSD1 in pediatric AML without otherwise favorable genetic markers. The role of quantitative PCR is also highlighted as a potential tool for

managing NUP98-NSD1 positive patients post-treatment. © 2013 Wiley Periodicals, Inc.

[56]

TÍTULO / TITLE: - Infections in Children and Adolescents With Juvenile Idiopathic Arthritis and Inflammatory Bowel Disease Treated With Tumor Necrosis Factor-alpha Inhibitors: Systematic Review of the Literature.

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

REVISTA / JOURNAL: - Clin Infect Dis. 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [1093/cid/cit489](#)

AUTORES / AUTHORS: - Toussi SS; Pan N; Walters HM; Walsh TJ

INSTITUCIÓN / INSTITUTION: - Division of Pediatric Infectious Diseases, Department of Pediatrics, Weill Cornell Medical Center.

RESUMEN / SUMMARY: - Tumor necrosis factor alpha (TNF-alpha) inhibitors are increasingly administered to children and adolescents with juvenile idiopathic arthritis (JIA) and pediatric inflammatory bowel disease (pIBD). Adult studies indicate that TNF-alpha inhibitors lead to an increased risk of serious infections compared to other disease-modifying antirheumatic drugs. We report herein a systematic literature review detailing the epidemiology and types of infections reported in children with JIA and pIBD treated with TNF-alpha inhibitors. The most frequently reported infections were mild and characterized as viral in etiology. Severe bacterial and fungal infections also occurred, but were less common and possibly associated with intrinsic risk factors and concurrent immunosuppressive therapy. Few pediatric patients developed Mycobacterium tuberculosis, likely due to effective screening. There were 8 infectious fatalities in children treated with TNF-alpha inhibitors. Overall, although rare, serious infections occur in immunocompromised children and adolescents with JIA and pIBD receiving TNF-alpha inhibitors.

[57]

TÍTULO / TITLE: - Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a Subgroup Analysis From the HOVON-65/GMMG-HD4 Trial.

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

REVISTA / JOURNAL: - Haematologica. 2013 Aug 30.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.087585](#)

AUTORES / AUTHORS: - Scheid C; Sonneveld P; Schmidt-Wolf IG; van der Holt B; El Jarari L; Bertsch U; Salwender H; Zweegman S; Blau IW; Vellenga E; Weisel K; Pfreundschuh M; Jie KS; Neben K; van de Velde H; Duehrsen U; Schaafsma MR; Lindemann W;

Kersten MJ; Peter N; Hanel M; Croockewit S; Martin H; Wittebol S; Bos GM; van Marwijk-Kooy M; Wijermans P; Goldschmidt H; Lokhorst HM

INSTITUCIÓN / INSTITUTION: - University of Cologne;

RESUMEN / SUMMARY: - Renal impairment is frequent in patients with multiple myeloma and correlates with inferior prognosis. This analysis evaluates the prognostic role of renal impairment in patients with myeloma treated with bortezomib before and after autologous stem cell transplantation within a prospective randomized phase III trial. 827 newly diagnosed myeloma patients in the HOVON-65/GMMG-HD4 trial were randomized to receive 3 cycles of vincristine, adriamycin, dexamethasone (VAD) or bortezomib, adriamycin, dexamethasone (PAD) followed by autologous stem cell transplantation and maintenance with thalidomide 50 mg daily (VAD-arm) or bortezomib 1.3 mg/m² every 2 weeks (PAD-arm). 746 patients had a baseline-serum creatinine less than 2 mg/dl (Durie-Salmon-stage A) and 81 had 2 mg/dl or higher (stage B). In myeloma patients with base line creatinine \geq 2 mg/dl the renal response rate was 63% in the VAD- arm and 81% in the PAD-arm (p=0.31). The overall myeloma response rate was 64% in the VAD-arm versus 89% in the PAD-arm with 13% CR in the VAD arm versus 36% in the PAD arm (p=0.01). Overall survival at 3 years for patients with base line creatinine \geq 2 mg/dl was 34% in the VAD-arm versus 74% in the PAD-arm (p<0.001) with a progression-free survival at 3 years of 16% in the VAD-arm versus 48% in the PAD-arm (p=0.004). Overall and progression-free survival in the PAD- arm were similar in patients with base line creatinine \geq 2 mg/dl or <2 mg/dl. We conclude that a bortezomib-containing treatment before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in patients with newly diagnosed multiple myeloma. The trial was registered at www.trialregister.nl as NTR213 and at www.controlled-trials.com as ISRCTN 64455289.

[58]

TÍTULO / TITLE: - Comparison of Prognostic Scores for Patients with Colorectal Cancer Peritoneal Metastases Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3204-2](#)

AUTORES / AUTHORS: - Cashin PH; Graf W; Nygren P; Mahteme H

INSTITUCIÓN / INSTITUTION: - Section of Surgery, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, peter.cashin@surgsci.uu.se.

RESUMEN / SUMMARY: - BACKGROUND: There are three prognostic scores for the cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) treatment of colorectal cancer peritoneal metastases: the newly introduced COREP

(colorectal peritoneal) score, the peritoneal surface disease severity score (PSDS), and the prognostic score (PS). The aim was to determine which prognostic score had the best prognostic value. METHODS: Between 2006 and 2010, a total of 77 patients with peritoneal metastases from colorectal cancer underwent CRS/HIPEC treatment. The COREP, PSDS, and PS scores were successfully applied to 56 patients (73 %) having sufficient data. The end points were prediction of open-and-close cases (n = 9), R1 resections (n = 41), and survival of <12 months (n = 18). Area under the receiver operating characteristic curves (accuracy) was compared. Subgroup analysis was performed on patients not previously used for the development of the COREP score (n = 24). Multivariable logistic regressions of the three end points were performed as well as Cox regression for overall survival. Furthermore, COREP and peritoneal cancer index were compared. RESULTS: For open-and-close case prediction, accuracy for the whole group (n = 56) and subgroup (n = 24) was 87 and 88 %, respectively for COREP; 66 and 77 % for PSDS; and 68 and 78 % for PS. For R1 resection prediction, accuracy was 81 and 81 %, 76 and 78 %, and 75 and 77 %, respectively. For prediction of survival of <12 months, accuracy was 83 and 84, 54 and 67 %, and 55 and 56 %, respectively. The COREP score was the only independent prognostic factor in all four multivariable analyses. A COREP score of ≥ 6 identified patients with poor survival more accurately than a PCI of >20 . CONCLUSIONS: The COREP score predicted open-and-close cases, R1 resections, and poor survival better than PSDS and PS. COREP better identifies patients with poor survival than intraoperative PCI.

[59]

TÍTULO / TITLE: - RAS Mutation Status Predicts Survival and Patterns of Recurrence in Patients Undergoing Hepatectomy for Colorectal Liver Metastases.

RESUMEN / SUMMARY: -

ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24018645

●● Enlace al texto completo (gratis o de pago) [1097/SLA.0b013e3182a5025a](https://doi.org/10.1097/SLA.0b013e3182a5025a)

AUTORES / AUTHORS: - Vauthey JN; Zimmiti G; Kopetz SE; Shindoh J; Chen SS; Andreou A; Curley SA; Aloia TA; Maru DM

INSTITUCIÓN / INSTITUTION: - Departments of *Surgical Oncology daggerGastrointestinal Medical Oncology double daggerHematopathology section signPathology, The University of Texas MD Anderson Cancer Center, Houston, TX.

RESUMEN / SUMMARY: - OBJECTIVE: To determine the impact of RAS mutation status on survival and patterns of recurrence in patients undergoing curative resection of colorectal liver metastases (CLM) after preoperative modern chemotherapy.

BACKGROUND: RAS mutation has been reported to be associated with aggressive tumor biology. However, the effect of RAS mutation on survival and patterns of recurrence after resection of CLM remains unclear. METHODS: Somatic mutations were analyzed using mass spectroscopy in 193 patients who underwent single-

regimen modern chemotherapy before resection of CLM. The relationship between RAS mutation status and survival outcomes was investigated. RESULTS: Detected somatic mutations included RAS (KRAS/NRAS) in 34 (18%), PIK3CA in 13 (7%), and BRAF in 2 (1%) patients. At a median follow-up of 33 months, 3-year overall survival (OS) rates were 81% in patients with wild-type versus 52.2% in patients with mutant RAS ($P = 0.002$); 3-year recurrence-free survival (RFS) rates were 33.5% with wild-type versus 13.5% with mutant RAS ($P = 0.001$). Liver and lung recurrences were observed in 89 and 83 patients, respectively. Patients with RAS mutation had a lower 3-year lung RFS rate (34.6% vs 59.3%, $P < 0.001$) but not a lower 3-year liver RFS rate (43.8% vs 50.2%, $P = 0.181$). In multivariate analyses, RAS mutation predicted worse OS [hazard ratio (HR) = 2.3, $P = 0.002$], overall RFS (HR = 1.9, $P = 0.005$), and lung RFS (HR = 2.0, $P = 0.01$), but not liver RFS ($P = 0.181$). CONCLUSIONS: RAS mutation predicts early lung recurrence and worse survival after curative resection of CLM. This information may be used to individualize systemic and local tumor-directed therapies and follow-up strategies.

[60]

TÍTULO / TITLE: - Excision-repair-cross-complement-1 protein as a prognostic factor in patients with advanced non-small cell lung cancer treated with platinum-based first-line chemotherapy.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Aug 11. pii: S0169-5002(13)00356-5. doi: 10.1016/j.lungcan.2013.08.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.08.001](#)

AUTORES / AUTHORS: - Vassalou H; Stathopoulos E; Fiolitaki G; Koutsopoulos A; Voutsina A; Georgoulas V; Mavroudis D

INSTITUCIÓN / INSTITUTION: - Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, Crete, Greece.

RESUMEN / SUMMARY: - Excision-repair-cross-complement-1 (ERCC1) protein expression in tumor cells has been associated with resistance to platinum compounds, the backbone of treatment in NSCLC. In the current study the impact of the tumoral ERCC1 protein expression on the outcome of patients with advanced stage NSCLC treated with platinum-based chemotherapy, was investigated. Ninety-four patients with inoperable stage III-IV NSCLC, treated with platinum-based first-line chemotherapy, were retrospectively analyzed. Pretreatment tumor samples were analyzed for ERCC1 protein expression using immunohistochemistry. Response to treatment, time to tumor progression (TTP), and overall survival (OS) were correlated with patients' clinicopathological characteristics and ERCC1 protein expression on tumor cells. ERCC1 protein low expression was detected in 39 (41.5%) patients and did not correlate with patients' clinicopathological characteristics or response to

chemotherapy. However, ERCC1 protein low expression showed a trend for better disease control rate ($p=0.059$), longer TTP (5.3 vs. 3.2 months; $p=0.051$) and significantly longer OS (18.7 vs. 9.7 months; $p=0.009$). ERCC1 could have a role in refining prognosis and thus individualizing chemotherapy for advanced stage NSCLC.

[61]

TÍTULO / TITLE: - Sequential Changes of Serum Anti-thyroglobulin Antibody Levels are a Good Predictor of Disease Activity in Thyroglobulin-Negative Patients with Papillary Thyroid Carcinoma.

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

REVISTA / JOURNAL: - Thyroid. 2013 Aug 25.

●● [Enlace al texto completo \(gratis o de pago\) 1089/thy.2012.0611](#)

AUTORES / AUTHORS: - Hsieh CJ; Wang PW

INSTITUCIÓN / INSTITUTION: - Division of Endocrinology and Metabolism, Department of Internal Medicine,, Kaohsiung Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, Kaohsiung , Taiwan ; c2607c@ms56.hinet.net.

RESUMEN / SUMMARY: - Objective: To investigate whether elevated and sequential changes in serum antithyroglobulin antibody (TgAb) levels are indicators of recurrence or persistence of papillary thyroid cancer (PTC) in patients with undetectable thyroglobulin (Tg). Methods: In 56 patients followed for more than 7 years, we recorded all serum TgAb levels (except the ones determined within one year after ^{131}I therapy or diagnostic scans) and evaluated their disease status. All patients had undergone total thyroidectomy and remnant ablation by ^{131}I , and they were positive for TgAb and had undetectable Tg during follow-up. The sequential changes of TgAb were defined as persistently high, increasing, persistently medium, decreasing, and decreasing to negative. Recurrence or persistence of PTC was defined as active disease as assessed by ^{131}I scanning, ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET), ultrasound, computed tomography, or surgical examination. Results: Of the 56 patients enrolled, 10 patients had persistent PTC and 12 patients had recurrent PTC at more than 1 year after total thyroidectomy and ^{131}I therapy. TgAb was persistently high in 4 patients (3 with active PTC), increasing in 6 (4 with active PTC), persistently medium in 16 patients (12 with active PTC), decreasing in 5 patients (none with active PTC), and decreased to negative in 25 patients (3 with active PTC). According to the trend, the patients with persistently high TgAb, increasing TgAb, and persistently medium TgAb had active disease more often ($p < 0.001$). In the multivariable regression analyses, the trend of TgAb change was a strong predictor of PTC activity ($p < 0.001$, $R^2 = -0.501$). The most common diagnostic procedures performed for active disease were neck ultrasound (21 patients) followed by ^{18}F -FDG PET (11 patients). The patients with autoimmune thyroid disease had better prognoses

than did the patients without autoimmune thyroid disease (18% active PTC vs. 53% active PTC, $p = 0.02$). Conclusion: The presence of TgAb is indicative of an active tumor. Sequential TgAb change is a good predictor of disease prognosis and is helpful for clinical decision-making.

PTPTPTP - JOURNAL ARTICLE ----- [62]

TÍTULO / TITLE: - Matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, B tenascin-C and ED-A fibronectin in dilated cardiomyopathy: Potential impact on disease progression and patients' prognosis.

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

REVISTA / JOURNAL: - Int J Cardiol. 2013 Aug 15. pii: S0167-5273(13)01530-1. doi: 10.1016/j.ijcard.2013.08.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijcard.2013.08.005](#)

AUTORES / AUTHORS: - Franz M; Berndt A; Neri D; Galler K; Grun K; Pormann C; Reinbothe F; Mall G; Schlattmann P; Renner A; Figulla HR; Jung C; Kuthe F

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine I, University Hospital Jena, Erlanger Allee 101, 07740 Jena, Germany. Electronic address: Marcus.Franz@med.uni-jena.de.

RESUMEN / SUMMARY: - BACKGROUND: Dilated cardiomyopathy (DCM) is associated with heart failure and increased mortality and there is no reliable biomarker to estimate patients' prognosis. During cardiac remodeling, an extensive reorganization of the extracellular matrix occurs. The study was aimed to investigate matrix metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 1 (TIMP-1) and fetal tenascin-C (B+ Tn-C) and fibronectin (ED-A+ Fn) variants known to be involved in that process. METHODS AND RESULTS: In 187 patients with DCM, levels of MMP-9, TIMP-1 and B+ Tn-C in serum as well as B+ Tn-C and ED-A+ Fn in tissue were quantified and subjected to univariate analysis. For all serum markers, concentrations above a calculated threshold were associated with decreased survival (MMP-9: $p=0.008$, TIMP-1: $p=0.001$, B+ Tn-C: $p<0.001$) and a significantly higher risk to die or undergo transplantation. In tissue, a reexpression of B+ Tn-C and ED-A+ Fn could be shown. Protein deposition levels of $\geq 4.5\%$ for B+ Tn-C and $\geq 2.1\%$ for ED-A+ Fn were associated with a significantly decreased survival ($p=0.001$ for B+ Tn-C, $p=0.031$ for ED-A+ Fn) and an increased risk to die or undergo transplantation. In a multivariate analysis, TIMP-1 is the superior parameter to predict transplantation free survival ($p=0.027$). CONCLUSIONS: Serum levels of MMP-9, TIMP-1 and B+ Tn-C and tissue levels of B+ Tn-C and ED-A+ Fn are promising markers for risk assessment. The reoccurrence of ED-A+ Fn and the availability of a human antibody usable as a vehicle for targeted drug delivery might be the basis for novel therapeutic strategies.

[63]

TÍTULO / TITLE: - Proline-rich tyrosine kinase 2 and its phosphorylated form pY881 are novel prognostic markers for non-small-cell lung cancer progression and patients' overall survival.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1252-63. doi: 10.1038/bjc.2013.439. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.439](#)

AUTORES / AUTHORS: - Kuang BH; Zhang MQ; Xu LH; Hu LJ; Wang HB; Zhao WF; Du Y; Zhang X

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, 651 East Dongfeng Road, Guangzhou 510060, China.

RESUMEN / SUMMARY: - Background:Our previous study revealed that proline-rich tyrosine kinase 2 (Pyk2) is implicated in both anchorage-independent growth and anoikis resistance in lung cancer cells. This study aims to explore the expression and clinical significance of Pyk2 and its phosphorylated forms in non-small-cell lung cancer (NSCLC).Methods:The mRNA and protein levels of Pyk2 or cancer stem cell markers (ALDH1a1, ABCG2 and Bmi-1) were either examined by reverse transcription-PCR or western blotting. An immunohistochemistry (IHC) assay was conducted to analyse the expression of Pyk2 and its phosphorylated forms in 128 NSCLC cases.Results:The levels of Pyk2 mRNA, total protein, and its phosphorylated form pY881 were higher in lung cancer lesions than in the paired noncancerous tissues. The IHC analysis showed the levels of the Pyk2 and Pyk2[pY881] proteins were highly expressed in 70 (54.7%) and 77 (60.2%) cases, respectively. Both Pyk2 and Pyk2[pY881] were independent prognostic factors for NSCLC patients. The gain and loss study of Pyk2 function revealed that Pyk2 could upregulate the expression of ALDH1a1, ABCG2 and Bmi-1 and enhance the ability of colony formation in soft agar assay in A549 and H460 cells.Conclusion:Both Pyk2 and phosphorylated Pyk2[pY881] are potential prognostic factors and therapeutic targets for NSCLC.

[64]

TÍTULO / TITLE: - Significance of deeper molecular responses in patients with chronic myeloid leukemia in early chronic phase treated with tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Am J Hematol. 2013 Aug 1. doi: 10.1002/ajh.23560.

●● Enlace al texto completo (gratis o de pago) [1002/ajh.23560](#)

AUTORES / AUTHORS: - Falchi L; Kantarjian HM; Wang X; Verma D; Quintas-Cardama A; O'Brien S; Jabbour EJ; Ravandi-Kashani F; Borthakur G; Garcia-Manero G; Verstovsek S; Burger JA; Luthra R; Cortes JE

INSTITUCIÓN / INSTITUTION: - Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas.

RESUMEN / SUMMARY: - Most patients with chronic myeloid leukemia (CML) in chronic phase (CP) treated with tyrosine kinase inhibitors (TKI) achieve complete cytogenetic response (CCyR). An increasing number of patients also achieve deep molecular responses (MR). We determined the frequency and significance of deep MR after TKI therapy for CML in CP. MR included: major molecular response (MMR), MR4, MR4.5, and undetectable transcripts (UND), i.e., BCR-ABL/ABL of ≤ 0.1 , ≤ 0.01 , $\leq 0.0032\%$, and undetectable transcripts, respectively. Four hundred eighty-three patients received imatinib 400 mg/day (IM400, 71, July 2000 to April 2001), imatinib 800 mg/day (IM800, 204, June 2001 to July 2005), nilotinib (106, July 2005 to date), or dasatinib (102, November 2005 to date). UND rates at 36 months were 18.1, 30.6, 29.2, and 28.6%, respectively. Patients achieving UND have superior transformation-free survival (TFS) and overall survival (OS) versus those obtaining \leq MMR, but not other MR levels. At the 18- and 24-month landmark analysis, patients achieving UND have no advantage in TFS and OS compared to those achieving a lesser degree of MR. Among patients achieving MR4.5, those who maintain it for ≥ 2 years (susMR4.5) have no additional benefit in TFS or OS. Most patients with early CP CML receiving TKI achieve MMR. BCR-ABL transcripts become undetectable in a significant fraction of them. Deeper MR at 18 or 24 months are not associated with a benefit in TFS or OS. Furthermore, achieving susMR4.5 does not appear to further reduce the risk of transformation or death. Am. J. Hematol., 2013. © 2013 Wiley Periodicals, Inc.

[65]

TÍTULO / TITLE: - Inhibiting the inhibitor: targeting vascular endothelial protein tyrosine phosphatase to promote tumor vascular maturation.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Aug 21;105(16):1163-5. doi: 10.1093/jnci/djt199. Epub 2013 Jul 30.

●● Enlace al texto completo (gratuito o de pago) [1093/jnci/djt199](#)

AUTORES / AUTHORS: - Kontos CD; Willett CG

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Department of Medicine, Division of Cardiology (CDK), Department of Pharmacology and Cancer Biology (CDK), and Department of Radiation Oncology (CGW), Duke University School of Medicine, Durham, NC.

[66]

TÍTULO / TITLE: - Pregnancies in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitor.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Oct;37(10):1216-21. doi: 10.1016/j.leukres.2013.07.020. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.020](https://doi.org/10.1016/j.leukres.2013.07.020)

AUTORES / AUTHORS: - Zhou L; You JH; Wu W; Li JM; Shen ZX; Wang AH

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Ruijin Hospital, Shanghai Institute of Hematology, Shanghai Jiao-Tong University School of Medicine, Shanghai 200025, China.

RESUMEN / SUMMARY: - We presented our experience in chronic myeloid leukemia (CML) patients who conceived children and/or became pregnant while receiving tyrosine kinase inhibitor (TKI). Among 7 male patients, 7 pregnancies resulted in the birth of 7 healthy babies. Among 18 female patients, 8 ended in elective abortion; 3 had spontaneous abortion, and 7 carried to term, resulting in the birth of 8 healthy babies. All children have normal growth and development. All patients remain in TKI therapy and in good response. It is suggested that female patients are advised to practice adequate contraception. No special precautions apply for male patients receiving TKI.

[67]

TÍTULO / TITLE: - Kinase inhibitors: A molecular target for myelodysplastic syndromes.

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

REVISTA / JOURNAL: - Nat Rev Drug Discov. 2013 Aug 30;12(9):664-5. doi: 10.1038/nrd4108.

●● Enlace al texto completo (gratis o de pago) [1038/nrd4108](https://doi.org/10.1038/nrd4108)

AUTORES / AUTHORS: - Tse MT

[68]

TÍTULO / TITLE: - Body mass index and prognosis of metastatic breast cancer patients receiving first line chemotherapy.

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

REVISTA / JOURNAL: - Cancer Epidemiol Biomarkers Prev. 2013 Aug 14.

●● Enlace al texto completo (gratis o de pago) [1158/1055-9965.EPI-13-0595](https://doi.org/10.1158/1055-9965.EPI-13-0595)

AUTORES / AUTHORS: - Gennari A; Nanni O; Puntoni M; Decensi A; Scarpi E; Conte P; Antonucci G; Amadori D; Bruzzi P

INSTITUCIÓN / INSTITUTION: - Medical Oncology Unit, Galliera Hospital.

RESUMEN / SUMMARY: - Background: The effect of body mass index (BMI) on the prognosis of metastatic breast cancer (MBC) has not been explored so far. Methods: The relationship between BMI (kg/m²), and progression free (PFS) or overall survival (OS) was assessed in 489 MBC patients enrolled in 3 clinical trials of first line chemotherapy. WHO BMI categories were used: normal 18.5-24.9 kg/m², overweight

25-29.9 kg/m², obese 30+ kg/m². Univariate PFS and OS curves were estimated; multivariate Cox analysis was performed adjusting for age, menopausal status, PS, hormonal status and site and number of metastases. Results: Overall, 39.9% of the patients were normal or underweight, 37.8% were overweight and 22.3% were obese. Median age was 57 years (range 25-73); median performance status (PS) was 0. Median PFS was 10.9 months (IQR 5.5 to 19.9) in normal weight women, 13.0 months (IQR 7.8 to 23.7) in overweight and 12.2 (IQR 7.1 to 23.0) in obese women, p=0.17. Median OS was 32.0 months (95% CI 14.5-88.3), versus 33.2 (95% CI 19.4-81.1) and 30.7 (95% CI 17.6-50.8) respectively. In multivariate analyses, no statistically significant association between BMI category and PFS or OS was observed. Conclusions: In this study BMI was not associated with the outcome of MBC patients treated with first line chemotherapy. Impact: The absence of any evidence in support of a prognostic role of obesity in MBC patients treated with chemotherapy, dietary restrictions, medical interventions aimed at reducing BMI/insulin resistance, or specific anticancer treatment strategies do not seem to be appropriate.

[69]

TÍTULO / TITLE: - Targeted delivery of proapoptotic peptides to tumor-associated macrophages improves survival.

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

REVISTA / JOURNAL: - Proc Natl Acad Sci U S A. 2013 Oct 1;110(40):15919-15924. Epub 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1073/pnas.1312197110](#)

AUTORES / AUTHORS: - Cieslewicz M; Tang J; Yu JL; Cao H; Motoyama K; Lieber A; Raines EW; Pun SH

INSTITUCIÓN / INSTITUTION: - Departments of Bioengineering and Medical Genetics, University of Washington, Seattle, WA 98195.

RESUMEN / SUMMARY: - Most current cancer therapies focus on killing malignant cells, but these cells are often genetically unstable and can become resistant to chemotherapy. Tumor-associated macrophages (TAMs) facilitate disease progression by promoting angiogenesis and tumor cell growth, as well as by suppressing the adaptive immune response. TAMs are therefore potential targets for adjuvant anticancer therapies. However, resident macrophages are critical to host defense, and preferential ablation of TAMs remains challenging. Macrophage activation is broadly categorized as classically activated, or M1, and alternatively activated, or M2, and TAMs in the tumor microenvironment have been shown to adopt the anti-inflammatory, M2-like phenotype. To date, there are no methods for specific molecular targeting of TAMs. In this work, we report the discovery of a unique peptide sequence, M2pep, identified using a subtractive phage biopanning strategy against whole cells. The peptide preferentially binds to murine M2 cells, including TAMs, with

low affinity for other leukocytes. Confocal imaging demonstrates the accumulation of M2pep in TAMs in vivo after tail vein injection. Finally, tail vein injection of an M2pep fusion peptide with a proapoptotic peptide delays mortality and selectively reduces the M2-like TAM population. This work therefore describes a molecularly targeted construct for murine TAMs and provides proof of concept of this approach as an anticancer treatment. In addition, M2pep is a useful tool for murine M2 macrophage identification and for modulating M2 macrophages in other murine models of disease involving M2 cells.

[70]

TÍTULO / TITLE: - Initial Biopsy Gleason Score as a Predictive Marker for Survival Benefit in Patients with Castration-resistant Prostate Cancer Treated with Docetaxel: Data from the TAX327 Study.

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

REVISTA / JOURNAL: - Eur Urol. 2013 Aug 11. pii: S0302-2838(13)00828-2. doi: 10.1016/j.eururo.2013.08.007.

●● Enlace al texto completo (gratis o de pago) 1016/j.eururo.2013.08.007

AUTORES / AUTHORS: - van Soest RJ; de Morree ES; Shen L; Tannock IF; Eisenberger MA; de Wit R

INSTITUCIÓN / INSTITUTION: - Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands. Electronic address: r.vansoest@erasmusmc.nl.

RESUMEN / SUMMARY: - BACKGROUND: Since 2004, docetaxel has been the standard first-line systemic therapy for patients with metastatic castration-resistant prostate cancer (mCRPC). With abiraterone recently becoming available in the predocetaxel setting, it is warranted to identify subgroups of patients who may obtain the greatest benefit from docetaxel and particularly qualify for receiving docetaxel as first-line treatment for mCRPC. OBJECTIVE: We aimed to identify factors that could characterize subgroups of patients who obtain the greatest benefit from the use of docetaxel. DESIGN, SETTING, AND PARTICIPANTS: TAX327 was multinational, randomized, phase 3 study that was conducted from 2000 to 2002 in 1006 men with mCRPC. INTERVENTION: Patients were randomized to receive docetaxel every 3 wk (D3), weekly docetaxel (D1), or mitoxantrone every 3 wk (M3), each with prednisone. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: We investigated whether patients with poorly differentiated tumors (Gleason score ≥ 7) at diagnosis had greater benefit from D3 compared with M3 than patients with better differentiated tumors (Gleason score ≤ 6). Using a Cox model, we compared overall survival (OS) between the treatment groups within each subgroup of Gleason score. RESULTS AND LIMITATIONS: The TAX 327 data showed that the OS benefit of D3 versus M3 was greater in patients with high-grade tumors (median OS: 18.9 vs 14.5 mo; $p=0.009$) than in patients with low-grade tumors (median OS: 21.6 vs 20.7 mo; $p=0.674$). Limitations

of a retrospective analysis apply. CONCLUSIONS: The survival benefit obtained with docetaxel is most pronounced in patients with high-Gleason-score tumors (Gleason ≥ 7). In a time of shifting paradigms in mCRPC, with abiraterone becoming available prior to docetaxel chemotherapy, Gleason score may help in selecting patients who obtain the greatest benefit from docetaxel as first-line treatment for mCRPC. Prospective validation of these findings is warranted.

[71]

TÍTULO / TITLE: - Increased expression of TBX2 is a novel independent prognostic biomarker of a worse outcome in colorectal cancer patients after curative surgery and a potential therapeutic target.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):688. doi: 10.1007/s12032-013-0688-3. Epub 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0688-3](#)

AUTORES / AUTHORS: - Han Y; Tu WW; Wen YG; Yan DW; Qiu GQ; Peng ZH; Zhou CZ

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Shanghai First People's Hospital, School of Medicine, Shanghai Jiao Tong University, 85 Wujin Road, Shanghai, 20080, China.

RESUMEN / SUMMARY: - T-box2 (TBX2) plays a critical role in embryonic development. Recently, deregulated expression of TBX2 has been implicated in several malignancies. However, the expression and the role of TBX2 in colorectal cancer (CRC) remain unclear. In this study, we found that TBX2 was obviously up-regulated in CRC in comparison with the corresponding normal mucosa at transcriptional and protein level. Up-expression of TBX2 was significantly associated with depth of tumor invasion ($P = 0.006$), distant metastasis ($P = 0.038$), advanced AJCC stage ($P = 0.008$), and relapse ($P = 0.003$). TBX2 was a significantly prognostic factor for decreased survival and increased disease recurrence independent of tumor stage (II, III stage) and functioned as a biomarker to identify prognosis of patients with CRC (OS: HR 2.154; 95 % CI 1.019-4.551; $P = 0.044$, DFS: HR 2.253; 95 % CI 1.109-4.575; $P = 0.025$). Furthermore, TBX2 could serve as a potential target of cancer drug therapy.

[72]

TÍTULO / TITLE: - Cross-validation analysis of the prognostic significance of mucin expression in patients with resected non-small cell lung cancer treated with adjuvant chemotherapy: Results from IALT, JBR.10 and ANITA.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Oct;82(1):149-55. doi: 10.1016/j.lungcan.2013.06.015. Epub 2013 Aug 4.

●● Enlace al texto completo (gratuito o de pago) [1016/j.lungcan.2013.06.015](https://doi.org/10.1016/j.lungcan.2013.06.015)

AUTORES / AUTHORS: - Graziano SL; Lacas B; Vollmer R; Kratzke R; Popper H; Filipits M; Seymour L; Shepherd FA; Rosell R; Veillard AS; Taron M; Pignon JP

INSTITUCIÓN / INSTITUTION: - Department of Medicine, State University of New York Upstate Medical University, Syracuse, NY, USA(2). Electronic address:

grazians@upstate.edu.

RESUMEN / SUMMARY: - INTRODUCTION: CALGB 9633 was a randomized trial of observation versus adjuvant chemotherapy for patients with stage IB non-small cell lung cancer (NSCLC). In CALGB 9633, the presence of mucin in the primary tumor was associated with shorter disease-free survival (DFS; hazard ratio (HR)=1.9, p=0.002) and overall survival (OS; HR=1.9, p=0.004). METHODS: To validate these results, mucin staining was performed on primary tumor specimens from 780 patients treated on IALT, 351 on JBR.10 and 150 on ANITA. The histochemical technique using mucicarmine was performed. The prognostic value of mucin for DFS and OS was tested in a Cox model stratified by trial and adjusted for clinical and pathological factors. A pooled analysis of all 4 trials was performed for the predictive value of mucin for benefit from adjuvant chemotherapy. RESULTS: The cross-validation group had 48% squamous, 37% adenocarcinoma and 15% other NSCLC compared with 29%, 56%, and 15%, respectively in CALGB. Among 1262 patients with assessable results, mucin was positive in IALT 24%, JBR.10 30%, ANITA 22% compared with 45% in CALGB. Histology was the only significant covariate (p<0.0001) in multivariate analysis with mucin seen more commonly in adenocarcinoma (56%) compared with squamous (5%) and other NSCLC (15%). Mucin was a borderline negative prognostic factor for DFS (HR=1.2 [1.0-1.5], p=0.06) but not significantly so for OS (HR=1.1 [0.9-1.4], p=0.25). Prognostic value did not vary according to histology: HR=1.3 [1.0-1.6] in adenocarcinoma vs. 1.6 [1.2-2.2] for DFS in other histology (interaction p=0.69). Mucin status was not predictive for benefit from adjuvant chemotherapy (test of interaction: DFS p=0.27; OS p=0.49). CONCLUSIONS: Mucin was less frequent in the cross-validation group due to its higher percentage of squamous cell carcinomas. The negative impact of mucin was confirmed for DFS but not for OS. Mucin expression was not predictive of overall survival benefit from adjuvant chemotherapy.

[73]

TÍTULO / TITLE: - Interrogation of ERG gene rearrangements in prostate cancer identifies a prognostic 10-gene signature with relevant implication to patients' clinical outcome.

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

REVISTA / JOURNAL: - BJU Int. 2013 Jun 5. doi: 10.1111/bju.12262.

●● Enlace al texto completo (gratuito o de pago) [1111/bju.12262](https://doi.org/10.1111/bju.12262)

AUTORES / AUTHORS: - Bismar TA; Alshalalfa M; Petersen LF; Teng LH; Gerke T; Bakkar A; Al-Mami A; Liu S; Dolph M; Mucci LA; Alhadj R

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Calgary, AB, Canada; Department of Oncology, University of Calgary, Calgary, AB, Canada; Southern Alberta Cancer Institute and Tom Baker Cancer Center, Calgary, AB, Canada.

RESUMEN / SUMMARY: - OBJECTIVES: ERG-gene rearrangement defines a distinct molecular subtype of PCA with potential biological and clinical implications. To identify a molecular signature reflective of the downstream effects of ERG-mediated transcriptional regulation with prognostic implication in patients with prostate cancer (PCA). MATERIAL AND METHODS: We used a singular value decomposition (SVD) bioinformatics approach to re-analyse gene expression data previously generated from 46 prostate tumours, and identified an ERG-like gene signature. The signature was validated on several patient cohorts and individual genes were correlated to ERG expression and PCA progression. RESULTS: An ERG-like 10-gene signature was identified and validated in PCA cohorts of the physician health study (p115) (n = 110) in addition to three independent public datasets, and was significantly associated with disease progression, biochemical recurrence and PCA-specific mortality. Patients with the ERG-like signature were significantly associated with disease recurrence on univariate (hazard ratio [HR] 2.6; 95% confidence interval [CI]:1.3-5.2; P = 0.004) and multivariate analysis (HR 2.3; 95% CI:1.1-4.6, P = 0.016) compared with patients without this signature. Within the group of patients with Gleason score (GS) 6 and 7 PCA, the signature added prognostic value beyond GS and identified patients at higher risk of cancer deaths more accurately than GS alone or in combination with ERG status. Protein expression of the 10 genes were significantly associated with ERG and disease progression regardless of ERG status. CONCLUSION: The characterized ERG-like signature was reflective of aggressive features of ERG-mediated transcription and was prognostically robust. The combination of this signature with clinicopathological variables should be validated prospectively to explore its clinical utility in stratifying patients with PCA and in identifying those at higher risk of metastatic and lethal disease.

[74]

TÍTULO / TITLE: - Vertebral Erosions Associated with Spinal Inflammation in Patients with Ankylosing Spondylitis Identified by Magnetic Resonance Imaging: Changes After 2 Years of Tumor Necrosis Factor Inhibitor Therapy.

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

REVISTA / JOURNAL: - J Rheumatol. 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [3899/jrheum.120533](https://doi.org/10.1093/rheumatology/ket120)

AUTORES / AUTHORS: - Baraliakos X; Listing J; Haibel H; Sieper J; Braun J

INSTITUCIÓN / INSTITUTION: - From the Rheumazentrum Ruhrgebiet, Herne, Ruhr-University Bochum; German Rheumatism Research Center, Berlin; and Department of

Rheumatology, University of Medicine Berlin, Campus Benjamin Franklin, Berlin, Germany.

RESUMEN / SUMMARY: - OBJECTIVE: Spinal inflammation and erosions have been described in magnetic resonance imaging (MRI) examinations of patients with ankylosing spondylitis (AS). MRI scoring systems have implemented these observations. METHODS: MRI scans (T1 or short-tau inversion recovery) from tumor necrosis factor-alpha blocker (anti-TNF) trials with patients with active AS (n = 22) were analyzed at baseline and after 2 years based on vertebral units (VU). The analysis was based on the prevalence of spinal erosions in relation to inflammation (active erosions) or without it (inactive erosions) as an outcome measure on MRI and their course under anti-TNF therapy. The results of MRI scoring systems that include (ASspiMRI) or exclude (Berlin score) erosions were also compared. RESULTS: At baseline, there were more VU with inflammation (33.7%) than with erosions irrespective of activity (10.6%). After 2 years, active erosions decreased to 3.7% while inflammation was seen in a total of 12% of VU - a reduction of 58.9% and 64.5%, respectively (both $p < 0.02$). The overall extent of erosions decreased from 10.6% at baseline to 5.6% at 2 years. At the patient level, 73% and 32% of patients showed active erosions ($p = 0.002$), while 100% and 64% of patients showed inflammation ($p = 0.029$) at baseline and 2 years, respectively. Both scoring systems showed similar improvement, independent of inclusion or exclusion of erosions. CONCLUSION: Inflammation with erosions was observed in the spine of most patients with AS but their contribution to changes observed upon anti-TNF therapy was small, indicating that erosions do not need to be included in quantitative scoring systems of inflammation. Spinal inflammation was still present after 2 years of anti-TNF therapy in two-thirds of patients.

[75]

TÍTULO / TITLE: - Improved therapeutic effect on malignant glioma with adenoviral suicide gene therapy combined with temozolomide.

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

REVISTA / JOURNAL: - Gene Ther. 2013 Sep 26. doi: 10.1038/gt.2013.46.

●● [Enlace al texto completo \(gratis o de pago\) 1038/gt.2013.46](#)

AUTORES / AUTHORS: - Stedt H; Samaranayake H; Pikkarainen J; Maatta AM; Alasaarela L; Airene K; Yla-Herttuala S

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology and Molecular Medicine, A. I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland.

RESUMEN / SUMMARY: - Malignant gliomas (MGs) are cancers with poor prognosis and limited therapeutic options. Herpes Simplex virus-1 thymidine kinase expressed from adenoviruses with prodrug ganciclovir (TK/GCV) is the best-characterized suicide gene therapy, whereas temozolomide (TMZ) is the first-line chemotherapy for MG.

However, the potential of their combination has not been studied thoroughly. The aim of this study was to evaluate the therapeutic response of this combination and to study whether addition of valproic acid (VPA) could benefit the treatment outcome. Efficacies of different treatments were first studied in vitro in BT4C rat MG cells. Therapeutic assessment in vivo was done in an immunocompetent rat MG model for treatment efficacy and toxicity. In vitro, VPA was able to significantly enhance cytotoxicity and increase adenovirus-mediated transduction efficiency up to sevenfold. In vivo, rats receiving TK/GCV+TMZ had notably smaller tumors and enhanced survival ($P < 0.001$) in comparison with control rats. However, VPA was not able to further enhance the treatment response in vivo. Leukocytopenia and thrombocytopenia were the major side effects. We conclude that careful optimization of the treatment schedules and doses of individual therapies are necessary to achieve an optimal therapeutic effect with TK/GCV+TMZ combination. No further in vivo benefit with VPA was observed. Gene Therapy advance online publication, 26 September 2013; doi:10.1038/gt.2013.46.

[76]

TÍTULO / TITLE: - Monocyte count at diagnosis is a prognostic parameter in diffuse large B-cell lymphoma: a large multicenter study involving 1191 patients, in the pre and post rituximab era.

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

REVISTA / JOURNAL: - Haematologica. 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.088161](https://doi.org/10.1007/s12096-013-0881-1)

AUTORES / AUTHORS: - Tadmor T; Bari A; Sacchi S; Marcheselli L; Liardo EV; Avivi I; Benyamini N; Attias D; Pozzi S; Cox MC; Baldini L; Brugiattelli M; Federico M; Polliack A

INSTITUCIÓN / INSTITUTION: - Bnai Zion Medical Center, Haifa, Faculty of Medicine, Israel;

RESUMEN / SUMMARY: - In this study we assessed the prognostic significance of absolute monocyte count and elected the best cut-off value at diagnosis, in a large cohort of patients with diffuse large B-cell lymphoma. Data were retrieved for therapy-naive patients with diffuse large B-cell lymphoma followed in Israel and Italy during 1993-2010. A final cohort of 1017 patients was analyzed with a median follow up of 48 months and a 5 year overall survival rate of 68%. The best absolute monocyte count cut-off level was $< 630/\text{mm}^3$ and the 5 years overall survival for these patients was 71% and 59% for those with $> 630/\text{mm}^3$ ($p = 0.0002$). Of the 1017 patients, 521 (51%) were treated with chemo-immunotherapy, and in this cohort, using multivariate analysis, elevated monocyte count retained a negative prognostic value even when adjusted for IPI (HR 1.54, $P = 0.009$). This large study shows that a simple parameter like absolute monocyte count ($> 630/\text{mm}^3$) can easily be used routinely in the evaluation of newly diagnosed diffuse large B-cell lymphoma to identify high-risk patients with a worse survival in the rituximab era.

[77]

TÍTULO / TITLE: - Profiling chronic myeloid leukemia patients reporting intentional and unintentional non-adherence to lifelong therapy with tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Jul 29. pii: S0145-2126(13)00230-0. doi: 10.1016/j.leukres.2013.07.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.003](#)

AUTORES / AUTHORS: - Efficace F; Rosti G; Cottone F; Breccia M; Castagnetti F; Iurlo A; Mandelli F; Bacarani M

INSTITUCIÓN / INSTITUTION: - Data Center and Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA), Rome, Italy. Electronic address: f.efficace@gimema.it.

RESUMEN / SUMMARY: - The main objective of this study was to outline key characteristics, including health-related quality of life (HRQOL) and symptoms, in 175 chronic myeloid leukemia (CML) patients reporting intentional or unintentional reasons for not fully adhering to imatinib therapy. There was a significant higher proportion of males in the unintentional group ($P=0.037$). Also, in this group patients were on average younger ($P=0.046$). Patients reporting intentional reasons had generally a worse HRQOL profile and a higher symptom severity than those who reported unintentional reasons for non-adherence. This study suggests that patients with suboptimal adherence are not a homogenous group, thus generalized approaches to improve medication-taking behaviors are not recommended.

[78]

TÍTULO / TITLE: - CEBPA single mutation can be a possible favorable prognostic indicator in NPM1 and FLT3-ITD wild-type acute myeloid leukemia patients with intermediate cytogenetic risk.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Sep 5. pii: S0145-2126(13)00296-8. doi: 10.1016/j.leukres.2013.08.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.08.014](#)

AUTORES / AUTHORS: - Park SH; Chi HS; Cho YU; Jang S; Park CJ

INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - The aim of this study was to evaluate the prognostic impact of CEBPA single mutation in acute myeloid leukemia (AML) patients with intermediate cytogenetic risk. CEBPA single and double mutations were detected in 11 (9.7%) and 17 (15.1%) of 113 NPM1 wild-type patients, but no CEBPA mutations were detected in

a group of 44 NPM1 mutated patients. Among patients with NPM1/FLT3-ITD wild-type, those with CEBPA double mutations (P=0.013 and 0.007 for overall survival and relapse-free survival, respectively) or a single mutation (P=0.039 and 0.020 for overall survival and relapse-free survival, respectively) demonstrated a favorable prognosis compared with CEBPA wild-type patients. Subsequent multivariate analysis confirmed the favorable prognostic impact of CEBPA single and double mutations. Despite the low statistical power of this study due to the small number of patients, our preliminary data suggest that CEBPA single mutation may be associated with favorable clinical outcomes in NPM1/FLT3-ITD wild-type AML patients with intermediate cytogenetic risk.

[79]

TÍTULO / TITLE: - Class III beta-tubulin overexpression within the tumor microenvironment is a prognostic biomarker for poor overall survival in ovarian cancer patients treated with neoadjuvant carboplatin/paclitaxel.

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

REVISTA / JOURNAL: - Clin Exp Metastasis. 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1007/s10585-013-9614-5](https://doi.org/10.1007/s10585-013-9614-5)

AUTORES / AUTHORS: - Roque DM; Buza N; Glasgow M; Bellone S; Bortolomai I; Gasparrini S; Cocco E; Ratner E; Silasi DA; Azodi M; Rutherford TJ; Schwartz PE; Santin AD

INSTITUCIÓN / INSTITUTION: - Division of Gynecologic Oncology, Yale University School of Medicine, 333 Cedar Street FMB 328, Box 208063, New Haven, CT, 06520, USA.

RESUMEN / SUMMARY: - Critics have suggested that neoadjuvant chemotherapy (NACT) followed by interval debulking may select for resistant clones or cancer stem cells when compared to primary cytoreduction. beta-tubulins are chemotherapeutic targets of taxanes and epothilones. Class III beta-tubulin overexpression has been linked to chemoresistance and hypoxia. Herein, we describe changes in class III beta-tubulin in patients with advanced ovarian carcinoma in response to NACT, in relationship to clinical outcome, and between patients who underwent NACT versus primary debulking; we characterize in vitro chemosensitivity to paclitaxel/patupilone of cell lines established from this patient population, and class III beta-tubulin expression following repeated exposure to paclitaxel. Using immunohistochemistry, we observed among 22 paired specimens obtained before/after NACT decreased expression of class III beta-tubulin following therapy within stroma ($p = 0.07$), but not tumor ($p = 0.63$). Poor median overall survival was predicted by high levels of class III beta-tubulin in both tumor (HR 3.66 [1.11,12.05], $p = 0.03$) and stroma (HR 4.53 [1.28,16.1], $p = 0.02$). Class III beta-tubulin expression by quantitative-real-time-polymerase-chain-reaction was higher among patients who received NACT ($n = 12$) compared to primary cytoreduction ($n = 14$) (mean +/- SD fold-change: 491.2 +/- 115.9 vs. 224.1 +/- 55.66, p

= 0.037). In vitro subculture with paclitaxel resulted in class III beta-tubulin upregulation, however, cell lines that overexpressed class III beta-tubulin remained sensitive to paclitaxel. Overexpression of class III beta-tubulin in patients dispositioned to NACT may thus identify an intrinsically aggressive phenotype, and predict poor overall survival and paclitaxel resistance. Decreases in stromal expression may represent normalization of the tumor microenvironment following therapy. Etoposide warrant study for patients who have received neoadjuvant carboplatin and paclitaxel.

[80]

TÍTULO / TITLE: - Association of gender, tumor necrosis factor inhibitor therapy, and myocardial infarction risk in patients with psoriasis.

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

REVISTA / JOURNAL: - J Am Acad Dermatol. 2013 Oct;69(4):650-1. doi: 10.1016/j.jaad.2013.04.035.

●● Enlace al texto completo (gratis o de pago) [1016/j.jaad.2013.04.035](https://doi.org/10.1016/j.jaad.2013.04.035)

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[81]

TÍTULO / TITLE: - Current clinical trials with polo-like kinase 1 inhibitors in solid tumors.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Nov;24(10):999-1006. doi: 10.1097/CAD.0000000000000007.

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

[1097/CAD.0000000000000007](https://doi.org/10.1097/CAD.0000000000000007)

AUTORES / AUTHORS: - Yim H

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, College of Pharmacy, Institute of Pharmaceutical Science and Technology, Hanyang University, Gyeonggi-do, Republic of Korea.

RESUMEN / SUMMARY: - Significant advances in cancer treatment have resulted from the targeted cancer therapy by understanding the process of malignant transformation. Polo-like kinase 1 (PLK1) has been investigated as a target for cancer therapy for several years. Recently, anticancer drug candidates targeting PLK1 have been developed. To investigate the significance of PLK1 inhibitors in cancer patients, the current clinical statuses of PLK1 inhibitors including BI 2536, volasertib, and GSK461364A were analyzed. Monotherapy with BI 2536, the first human study of PLK1

inhibitors, has been terminated now, but its combinational study is still available in several solid tumors. The second-generation PLK1 inhibitor volasertib has an improved pharmacokinetic profile, safety, and efficacy, which is currently being developed under phase I/II. GSK461364 has shown a greater sensitive antitumor effect in p53-mutated cancer compared with that of p53-wild type cancer cells in a preclinical study. However, it has to be coadministered with an anticoagulator because of the high incidence of venous thrombotic emboli in clinical studies. PLK1 inhibitors showed a favorable pharmacokinetic profile, safety, and efficacy in patients with solid tumors. Further investigation with the use of PLK1 inhibitors in cancer patients who have mutated p53 or Ras and a high level of PLK1 as biomarkers is needed to consider the context and evaluation criteria of therapy.

[82]

TÍTULO / TITLE: - Investigation of Complement Activation Product C4d as a Diagnostic and Prognostic Biomarker for Lung Cancer.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Sep 18;105(18):1385-1393. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt205](#)

AUTORES / AUTHORS: - Ajona D; Pajares MJ; Corrales L; Agorreta J; Lozano MD; Torre W; Massion PP; de-Torres JP; Jantus-Lewintre E; Camps C; Zulueta JJ; Montuenga LM; Pio R

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Division of Oncology, Center for Applied Medical Research, Pamplona, España (DA, MJP, LC, JA, LMM, RP); Department of Histology and Pathology (MJP, JA, LMM) and Department of Biochemistry and Genetics (RP) School of Medicine, University of Navarra, Pamplona, España; Department of Oncology (JLP), Department of Pathology (MDL), Department of Thoracic Surgery (WT), Department of Pulmonary Medicine (JPdT, JJZ) Clinica Universidad de Navarra, Pamplona, España; Thoracic Program, Vanderbilt Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN (PPM); Department of Medicine, University of Valencia, Valencia, España (CC); Department of Medical Oncology, Hospital General Universitario de Valencia, Valencia, España (CC); Molecular Oncology Laboratory, Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, España (EJL).

RESUMEN / SUMMARY: - BACKGROUND: There is a medical need for diagnostic biomarkers in lung cancer. We evaluated the diagnostic performance of complement activation fragments. METHODS: We assessed complement activation in four bronchial epithelial and seven lung cancer cell lines. C4d, a degradation product of complement activation, was determined in 90 primary lung tumors; bronchoalveolar lavage supernatants from patients with lung cancer (n = 50) and nonmalignant respiratory

diseases (n = 22); and plasma samples from advanced (n = 50) and early lung cancer patients (n = 84) subjects with inflammatory lung diseases (n = 133), and asymptomatic individuals enrolled in a lung cancer computed tomography screening program (n = 190). Two-sided P values were calculated by Mann-Whitney U test. RESULTS: Lung cancer cells activated the classical complement pathway mediated by C1q binding that was inhibited by phosphomonoesters. Survival was decreased in patients with high C4d deposition in tumors (hazard ratio [HR] = 3.06; 95% confidence interval [CI] = 1.18 to 7.91). C4d levels were increased in bronchoalveolar lavage fluid from lung cancer patients compared with patients with nonmalignant respiratory diseases (0.61+/-0.87 vs 0.16+/-0.11 microg/mL; P < .001). C4d levels in plasma samples from lung cancer patients at both advanced and early stages were also increased compared with control subjects (4.13+/-2.02 vs 1.86+/-0.95 microg/mL, P < 0.001; 3.18+/-3.20 vs 1.13+/-0.69 microg/mL, P < .001, respectively). C4d plasma levels were associated with shorter survival in patients at advanced (HR = 1.59; 95% CI = 0.97 to 2.60) and early stages (HR = 5.57; 95% CI = 1.60 to 19.39). Plasma C4d levels were reduced after surgical removal of lung tumors (P < .001) and were associated with increased lung cancer risk in asymptomatic individuals with (n = 32) or without lung cancer (n = 158) (odds ratio = 4.38; 95% CI = 1.61 to 11.93). CONCLUSIONS: Complement fragment C4d may serve as a biomarker for early diagnosis and prognosis of lung cancer.

[83]

TÍTULO / TITLE: - Prognostic relevance of ubiquitin C-terminal hydrolase L1 (UCH-L1) mRNA and protein expression in breast cancer patients.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Oct;139(10):1745-55. doi: 10.1007/s00432-013-1496-z. Epub 2013 Aug 31.

●● Enlace al texto completo (gratuito o de pago) [1007/s00432-013-1496-z](#)

AUTORES / AUTHORS: - Schroder C; Milde-Langosch K; Gebauer F; Schmid K; Mueller V; Wirtz RM; Meyer-Schwesinger C; Schluter H; Sauter G; Schumacher U

INSTITUCIÓN / INSTITUTION: - Department of Gynaecology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, ch.schroeder@uke.de.

RESUMEN / SUMMARY: - PURPOSE: The ubiquitin C-terminal hydrolase L1 (UCH-L1) belongs to the family of deubiquitinating enzymes. It is overexpressed in various tumour entities and associated with metastases formation in some solid tumours. However, only limited information about its role in breast cancer is available. The aim of this study was to examine the UCH-L1 expression in primary breast cancer and to determine its relevance as a potential prognostic marker. METHODS: We investigated both UCH-L1 mRNA expression in microarray data from 182 primary mammary carcinomas and UCH-L1 protein expression using a tissue microarray containing

samples from 1,622 breast cancer patients. RESULTS: With both methods, high UCH-L1 expression correlated significantly with negative oestrogen receptor and progesterone receptor status and advanced tumour stage. Moreover by Kaplan-Meier analysis, high UCH-L1 mRNA and protein expression correlated with a significantly shorter overall survival. CONCLUSION: The data of our study suggest that high levels of UCH-L1 expression indicate a more aggressive tumour behaviour and might represent a potential target in breast cancer treatment.

[84]

TÍTULO / TITLE: - Factors Predicting Late Recurrence for Estrogen Receptor-Positive Breast Cancer.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Oct 2;105(19):1504-1511. Epub 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt244](#)

AUTORES / AUTHORS: - Sestak I; Dowsett M; Zabaglo L; Lopez-Knowles E; Ferree S; Cowens JW; Cuzick J

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University, London, UK (IS, JC); Academic Department of Biochemistry, Royal Marsden Hospital, London, UK (MD, LZ, EL-K); NanoString Technologies, Seattle, WA (SF, JWC).

RESUMEN / SUMMARY: - BACKGROUND: Adjuvant endocrine therapy beyond 5 years reduces recurrence in patients with estrogen receptor-positive breast cancer. We have previously shown that immunohistochemical markers (IHC4) and two gene expression profile tests (recurrence score [RS] and PAM50 risk of recurrence [ROR]) are associated with time to distant recurrence, and we have now assessed the value of each of these scores and routine clinical variables for predicting outcome, specifically in years 5 to 10. METHODS: We used univariate and multivariable proportional hazards models to determine the prognostic value of all variables and scores (IHC4, RS, ROR) for distant recurrence, separately in years 0 to 5 and specifically for years 5 to 10 for all patients. All statistical tests were two-sided. RESULTS: Nodal status and tumor size were at least as strong in years 5 to 10 as in years 0 to 5 (nodal status, years 5-10: $\chi^2 = 21.72$ vs years 0-5: $\chi^2 = 11.08$, both $P < .001$; tumor size, years 5-10: $\chi^2 = 10.52$ vs years 0-5: $\chi^2 = 10.82$, both $P = .001$). Ki67 and the overall IHC4 score were the only statistically significant biomarkers related to distant recurrence univariably in the 5 to 10 year period ($\chi^2 = 8.67$, $\chi^2 = 13.22$, respectively). The ROR score was the strongest molecular prognostic factor in the late follow-up period ($\chi^2 = 16.29$; $P < .001$), whereas IHC4 ($\chi^2 = 7.41$) and RS ($\chi^2 = 5.55$) were only weakly prognostic in this period. Similar results were seen for all subgroups and for all recurrences. CONCLUSIONS: None of the IHC4 markers provided statistically significant prognostic

information in years 5 to 10, except for nodal status and tumor size. ROR gave the strongest prognostic information in years 5 to 10. These results may help select patients who could benefit most from hormonal therapy beyond 5 years of treatment.

[85]

TÍTULO / TITLE: - High CC chemokine receptor 7 expression improves postoperative prognosis of lung adenocarcinoma patients.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1100-8. doi: 10.1038/bjc.2013.440. Epub 2013 Aug 6.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.440](#)

AUTORES / AUTHORS: - Itakura M; Terashima Y; Shingyoji M; Yokoi S; Ohira M; Kageyama H; Matui Y; Yoshida Y; Ashinuma H; Moriya Y; Tamura H; Harigaya K; Matushima K; Iizasa T; Nakagawara A; Kimura H

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Disease, Chiba Cancer Center, 662-2 Nitona-cho, Chuo-ku, Chiba 260-8717, Japan.

RESUMEN / SUMMARY: - Background: Chemokines and chemokine receptors not only have significant roles in cancer metastasis and tumorigenesis but also act as antitumour agents. The interaction between the Crk-like adaptor protein (CrkL), which is encoded by the CRKL gene, and non-receptor tyrosine kinase c-ABL is reported to transform many cells into malignant cells. We examined the effects of CC chemokine receptor 7 (CCR7), CCR7 ligands and CrkL and c-ABL in lung adenocarcinoma. Methods: One hundred and twenty patients with lung adenocarcinoma were included in this historical cohort analysis. We examined CCR7 and CCR7 ligands and CrkL and c-ABL mRNA expressions in surgically resected lung adenocarcinoma specimens and evaluated their contribution to prognosis, and the relationship with epidermal growth factor receptor (EGFR) and TP53 mutations. Results: High CCR7 mRNA expressions indicated better prognoses than those of the groups with low CCR7 mRNA expressions (P=0.007, HR=2.00, 95% CI of ratio: 1.22-3.31). In lung adenocarcinoma, CrkL and c-ABL mRNAs were related to CCR7 mRNA expression (P<0.0001). CrkL and c-ABL mRNA expressions were influenced by EGFR mutations. A high expression of CCL19 was a good prognostic factor of lung adenocarcinoma. Conclusion: We propose that CCR7 and CCL19 are clinically good prognostic factors and that CCR7 is strongly related to CrkL and c-ABL kinase mRNA expression in lung adenocarcinoma.

[86]

TÍTULO / TITLE: - Protein expression and methylation of DNA repair genes hMLH1, hMSH2, MGMT and BRCA1 and their correlation with clinicopathological parameters and prognosis in basal-like breast cancer.

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

REVISTA / JOURNAL: - Histopathology. 2013 Jul 3. doi: 10.1111/his.12220.

●● Enlace al texto completo (gratis o de pago) [1111/his.12220](#)

AUTORES / AUTHORS: - Alkam Y; Mitomi H; Nakai K; Himuro T; Saito T; Takahashi M; Arakawa A; Yao T; Saito M

INSTITUCIÓN / INSTITUTION: - Department of Breast Oncology, Juntendo University School of Medicine, Tokyo, Japan; Department of Human Pathology, Juntendo University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - AIMS: Basal-like breast cancer (BLBC) is characterized by aggressive behaviour; its genesis is the perturbation of DNA repair as a consequence of BRCA1 methylation or mutation. We comparatively evaluated alterations of DNA repair proteins and p53 between BLBC and non-BLBC cases. METHODS AND RESULTS: Tumour sections from 104 BLBC and 89 non-BLBC patients were immunostained for hMLH1, hMSH2, MGMT, BRCA1 and p53. Methylation status of DNA repair genes was analysed by methylation-specific PCR, and p53 mutation was examined by direct sequencing. Immunoreactive levels of hMLH1 and MGMT were lower in BLBC, whereas the levels of hMSH2 and p53 were higher, compared to non-BLBC ($P \leq 0.014$). Reduced expression of hMLH1 [hazard ratio (HR) 5.26, $P = 0.001$] and preserved expression of MGMT (HR 2.58, $P = 0.039$) proved to be independent predictors of poor survival in BLBC patients. DNA repair genes were methylated in approximately 20-40% of BLBCs without a significant relationship between their methylation and p53 mutation. BRCA1 methylation was associated with the loss of its protein expression ($P = 0.004$). MGMT methylation was linked to larger tumour size ($P < 0.001$). CONCLUSIONS: Perturbations of the DNA repair system might be different between BLBC and non-BLBC. Alterations of hMLH1 and MGMT appear important for tumour progression and survival in BLBC patients.

[87]

TÍTULO / TITLE: - C-reactive protein predicts fatigue independently of depression in breast cancer patients prior to chemotherapy.

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

REVISTA / JOURNAL: - Brain Behav Immun. 2013 Aug 6. pii: S0889-1591(13)00411-X. doi: 10.1016/j.bbi.2013.07.177.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbi.2013.07.177](#)

AUTORES / AUTHORS: - Pertl MM; Hevey D; Boyle NT; Hughes MM; Collier S; O'Dwyer AM; Harkin A; Kennedy MJ; Connor TJ

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RESUMEN / SUMMARY: - Heightened inflammatory activity has been proposed as a mechanism for the development of cancer-related fatigue (CRF), a common and distressing condition that can negatively affect quality of life. Inflammation is also implicated in the pathogenesis of depression, and depression is a strong predictor of CRF. Thus, the role of the pro-inflammatory cytokine network in CRF may be mediated by depression or both conditions may share similar underlying physiological processes. The current study investigated associations between fatigue, depression and inflammatory cytokine (IFN-gamma, IL-6, TNF-alpha) and CRP concentrations, as well as kynurenine pathway (KP) activation, in 61 breast cancer patients prior to chemotherapy. Changes in inflammatory markers and KP activation over time were also explored, and associations with changes in fatigue and depression were examined. Higher levels of CRP were significantly correlated with fatigue and depression before chemotherapy; nevertheless, CRP predicted fatigue independently of depression. Although greater kynurenine concentrations were associated with increased immune activation, there was no evidence that the KP played a role in fatigue or depression. Furthermore, no relationships emerged between either fatigue or depression and IFN-gamma, IL-6, or TNF-alpha before chemotherapy. Nevertheless, kynurenine levels pre- and post-treatment significantly predicted changes in depression, suggesting that heightened KP activation may contribute to depressive symptoms in patients treated for cancer. In addition, IL-6 significantly covaried with fatigue. These preliminary findings provide some support for the idea that low-grade inflammation contributes to the development of CRF, independently of depression; however, there was no evidence that this is mediated by KP activity.

[88]

TÍTULO / TITLE: - A phase 1 study of the heat shock protein 90 inhibitor retaspimycin hydrochloride (IPI-504) in patients with gastrointestinal stromal tumors or soft tissue sarcomas.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0953](#)

AUTORES / AUTHORS: - Wagner AJ; Rosen LS; Morgan JA; George M D S; Gordon M; Dunbar J; Normant E; Grayzel D; Demetri GD

INSTITUCIÓN / INSTITUTION: - Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute.

RESUMEN / SUMMARY: - PURPOSE: Heat shock protein 90 (Hsp90) is required for the proper folding, function, and stability of various client proteins, two of which (KIT and PDGFRalpha) are critical in the pathogenesis and progression of gastrointestinal

stromal tumors (GIST). This phase 1 study investigated the safety and maximum tolerated dose (MTD) of retaspimycin hydrochloride (IPI-504), a novel potent and selective Hsp90 inhibitor, in patients with metastatic and/or unresectable GIST or other soft-tissue sarcomas (STS). EXPERIMENTAL DESIGN: IPI-504 was administered intravenously at doses ranging from 90 to 500 mg/m² twice weekly for 2 weeks on/1 week off. Safety, pharmacokinetic, and pharmacodynamic profiles were determined. Response was assessed by Response Evaluation Criteria for Solid Tumors (RECIST) 1.0 and optionally via 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) imaging. RESULTS: Fifty-four patients received IPI-504; 37 with GIST and 17 with other STS. The MTD was 400 mg/m² twice weekly for 2 weeks on/1 week off. Common related adverse events were fatigue (59%), headache (44%), and nausea (43%). Exposure to IPI-504, 17-AAG, and 17-AG increased with IPI-504 dose. Stable disease (SD) was observed in 70% (26/37) of patients with GIST and 59% (10/17) of patients with STS. There was one confirmed partial response (PR) in a patient with GIST and one PR in a patient with liposarcoma. Metabolic partial responses occurred in 11/29 (38%) of GIST patients. CONCLUSIONS: In this study of advanced GIST or other STS, IPI-504 was generally well-tolerated with some evidence of anti-tumor activity, serving as a clinical proof-of-concept that HSP90 inhibition remains a promising strategy.

[89]

TÍTULO / TITLE: - The code structure of the p53 DNA-binding domain and the prognosis of breast cancer patients.

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

REVISTA / JOURNAL: - Bioinformatics. 2013 Sep 12.

●● [Enlace al texto completo \(gratis o de pago\) 1093/bioinformatics/btt497](#)

AUTORES / AUTHORS: - Sato K; Hara T; Ohya M

INSTITUCIÓN / INSTITUTION: - Department of Information Science, Tokyo University of Science, Noda, Chiba 278-8510, Japan.

RESUMEN / SUMMARY: - MOTIVATION: The tumor-suppressor gene TP53 mutations are diverse in the central region encoding the DNA-binding domain. It has not been clear whether the prognostic significance for survival in breast cancer patients is the same for all types of mutations. Are there specific types of mutations carrying a worse prognosis? To understand the correlation between the mutations in the gene encoding the DNA-binding domain and the prognosis of breast cancer, we studied the code structure of the DNA-binding domain of breast cancer patients by using various artificial codes in information transmission. RESULTS: We indicated that the prognostic significance of all types of mutations in the DNA-binding domain is not the same, and that the DNA-binding domain having a certain code structure is important for estimating the prognosis of breast cancer patients. CONTACT: keiko@is.noda.tus.ac.jp or hara@is.noda.tus.ac.jp.

[90]

TÍTULO / TITLE: - Granulocyte Macrophage-Colony Stimulation Factor Promotes the Immunosuppressive Activity of Glioma-Infiltrating Myeloid Cells through Interleukin-4 Receptor-alpha

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

REVISTA / JOURNAL: - Cancer Res. 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-4124](#)

AUTORES / AUTHORS: - Kohanbash G; McKaveney K; Sakaki M; Ueda R; Mintz AH; Amankulor N; Fujita M; Ohlfest JR; Okada H

INSTITUCIÓN / INSTITUTION: - Department of Neurological Surgery, University of Pittsburgh.

RESUMEN / SUMMARY: - Malignant gliomas, such as glioblastoma, are lethal cancers in the brain and heavily infiltrated by myeloid cells. Interleukin-4 receptor-alpha (IL-4Ralpha) is known to mediate immunosuppressive functions of myeloid cells, and polymorphisms in the IL-4Ralpha gene are associated with altered glioma risk and prognosis. We therefore sought to determine the role of IL-4Ralpha in glioma development. In both mouse de novo gliomas and human glioblastoma cases, IL-4Ralpha is up-regulated on glioma-infiltrating myeloid cells but not in the periphery or normal brains. Mice deficient for IL-4Ralpha gene demonstrate slower growth of glioma associated with reduced production of arginase in the glioma microenvironment. In vitro studies with bone marrow-derived myeloid cells show that IL-4Ralpha mediates IL-13-induced production of arginase, which is critical for the T-cell suppressing function of myeloid cells. Furthermore, glioma-derived myeloid cells suppress T-cell proliferation in an IL-4Ralpha-dependent manner (myeloid-derived suppressor cells). Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a central role for the induction of IL-4Ralpha expression on myeloid cells, and is up-regulated in both human and mouse glioma environments compared with normal brains or peripheral blood samples. Our data demonstrate a novel GM-CSF-induced immunosuppression mechanism in the glioma microenvironment via up-regulation of IL-4Ralpha.

[91]

TÍTULO / TITLE: - Use of Early Tumor Shrinkage to Predict Long-Term Outcome in Metastatic Colorectal Cancer Treated With Cetuximab.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.42.8532](#)

AUTORES / AUTHORS: - Piessevaux H; Buyse M; Schlichting M; Van Cutsem E; Bokemeyer C; Heeger S; Tejpar S

INSTITUCIÓN / INSTITUTION: - Hubert Piessevaux, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels; Marc Buyse, International Drug Development Institute, Louvain-la-Neuve; Eric Van Cutsem and Sabine Tejpar, University Hospital Gasthuisberg, Leuven, Belgium; Michael Schlichting and Steffen Heeger, Merck KGaA, Darmstadt; and Carsten Bokemeyer, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

RESUMEN / SUMMARY: - **PURPOSE:** Early tumor shrinkage (ETS) is associated with long-term outcome in patients with chemorefractory metastatic colorectal cancer (mCRC) receiving cetuximab. This association was investigated in the first-line setting in the randomized CRYSTAL and OPUS mCRC trials, after controlling for KRAS tumor mutation status. **METHODS:** Radiologic assessments at week 8 were used to calculate the relative change in the sum of the longest diameters of the target lesions. Time-dependent receiver operating characteristics provided Ctau-indices (time-dependent c-index). Cox regression models and subpopulation treatment effect pattern plot analysis investigated associations between ETS (radiologic tumor size decrease at week 8) and survival and progression-free survival (PFS). **RESULTS:** In both trials, in patients with KRAS wild-type mCRC, Ctau values for PFS and survival were higher ($P < .001$) in those receiving chemotherapy plus cetuximab versus chemotherapy alone, indicating a stronger predictive value of ETS for long-term outcome in these patients. In the CRYSTAL and OPUS trials, respectively, the cutoff value of $ETS \geq 20\%$ ($v < 20\%$) identified patients with KRAS wild-type mCRC receiving chemotherapy plus cetuximab with longer PFS (medians 14.1 v 7.3 months, hazard ratio [HR] = 0.32; $P < .001$, and medians 11.9 v 5.7 months, HR = 0.22; $P < .001$) and survival (medians 30.0 v 18.6 months, HR = 0.53; $P < .001$ and medians 26.0 v 15.7 months, HR = 0.43; $P = .006$). **CONCLUSION:** ETS was significantly associated with long-term outcome in patients with KRAS wild-type mCRC treated first-line with chemotherapy plus cetuximab. Validation in prospective trials is required to assess the value of this on-treatment marker in the clinical decision-making process.

[92]

TÍTULO / TITLE: - Serum miR-200c Is a Novel Prognostic and Metastasis-Predictive Biomarker in Patients With Colorectal Cancer.

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

REVISTA / JOURNAL: - Ann Surg. 2013 Aug 26.

●● [Enlace al texto completo \(gratis o de pago\) 1097/SLA.0b013e3182a6909d](#)

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

INSTITUCIÓN / INSTITUTION: - *Gastrointestinal Cancer Research Laboratory, Division of Gastroenterology, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX; and daggerDepartment of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Graduate School of Medicine, Mie University, Mie, Japan.

RESUMEN / SUMMARY: - **OBJECTIVES::** To evaluate the ability of epithelial-to-mesenchymal transition-related microRNAs (miRNAs) as serum biomarkers for prognosis and prediction of metastasis in patients with colorectal cancer (CRC). **BACKGROUND::** Epithelial-to-mesenchymal transition-related miRNAs drive CRC progression and metastasis. However, their potential as serum biomarkers in CRC has not been studied. **METHODS::** This was a 3-phase study using 446 colorectal specimens. In the first phase, we selected candidate miRNAs associated with metastasis by analyzing the expression of 4 miR-200 family members (miR-200b, -200c, -141, and -429) in serum samples from 12 patients with stage I and IV CRC. The second phase involved independent validation of candidate miRNAs in serum from 182 patients with CRC and 24 controls. Finally, we analyzed expression in matched 156 tumor tissues from 182 patients with CRC and an independent set of 20 matched primary CRC and corresponding liver metastases to identify the source of circulating miRNAs. **RESULTS::** After initial screening, miR-200c was selected as the candidate serum miRNA best associated with metastasis. Validation analysis revealed that serum miR-200c levels were significantly higher in stage IV than in stage I-III CRCs. High serum miR-200c demonstrated a significant positive correlation with lymph node metastasis, distant metastasis, and prognosis ($P = 0.0026$, $P = 0.0023$, and $P = 0.0064$, respectively). More importantly, serum miR-200c was an independent predictor for lymph node metastasis (odds ratio: 4.81, 95% confidence interval: 1.98-11.7, $P = 0.0005$) and tumor recurrence (hazard ratio: 4.51, 95% confidence interval: 1.56-13.01, $P = 0.005$) and emerged as an independent prognostic marker for CRC (hazard ratio: 2.67, 95% confidence interval: 1.28-5.67, $P = 0.01$). **CONCLUSIONS::** Serum miR-200c has strong potential to serve as a noninvasive biomarker for CRC prognosis and predicting metastasis.

[93]

TÍTULO / TITLE: - Inhibition of amyloid precursor protein processing enhances gemcitabine-mediated cytotoxicity in pancreatic cancer cells.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Sep 10.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.459255](https://doi.org/10.1074/jbc.M113.459255)

AUTORES / AUTHORS: - Woods NK; Padmanabhan J

INSTITUCIÓN / INSTITUTION: - University of South Florida, United States.

RESUMEN / SUMMARY: - Pancreatic adenocarcinoma or pancreatic cancer is often diagnosed at a very late stage at which point treatment options are minimal. Current chemotherapeutic interventions prolong survival marginally, thereby emphasizing the acute need for better treatment options to effectively manage this disease. Studies from different laboratories have shown that the Alzheimer disease associated Amyloid Precursor Protein (APP) is overexpressed in various cancers but its significance is not known. Here we sought to determine the role of APP in pancreatic cancer cell survival and proliferation. Our results show that pancreatic cancer cells secrete high levels of sAPP-alpha, the alpha-secretase cleaved ectodomain fragment of APP, as compared to normal non-cancerous cells. Treatment of cells with batimastat or GI254023X, inhibitors of the alpha-secretase ADAM10, prevented sAPP-alpha generation and reduced cell survival. Additionally, inhibition of sAPP-alpha significantly reduced anchorage independent growth of the cancer cells. The effect of batimastat on cell survival and colony formation was enhanced when sAPP-alpha downregulation was combined with gemcitabine treatment. Moreover, treatment of batimastat-treated cells with recombinant sAPP-alpha reversed the inhibitory effect of the drug thereby indicating that sAPP-alpha can indeed induce proliferation of cancer cells. Downregulation of APP and ADAM10 brought about similar results, as did batimastat treatment, thereby confirming that APP processing is important for growth and proliferation of these cells. These results suggest that inhibition of sAPP-alpha generation might enhance the effectiveness of the existing chemotherapeutic regimen for a better outcome.

[94]

TÍTULO / TITLE: - Systems analysis of apoptosis protein expression allows the case-specific prediction of cell death responsiveness of melanoma cells.

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

REVISTA / JOURNAL: - Cell Death Differ. 2013 Aug 9. doi: 10.1038/cdd.2013.106.

●● Enlace al texto completo (gratis o de pago) [1038/cdd.2013.106](#)

AUTORES / AUTHORS: - Passante E; Wurstle ML; Hellwig CT; Leverkus M; Rehm M

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RESUMEN / SUMMARY: - Many cancer entities and their associated cell line models are highly heterogeneous in their responsiveness to apoptosis inducers and, despite a detailed understanding of the underlying signaling networks, cell death susceptibility currently cannot be predicted reliably from protein expression profiles. Here, we demonstrate that an integration of quantitative apoptosis protein expression data with pathway knowledge can predict the cell death responsiveness of melanoma cell lines. By a total of 612 measurements, we determined the absolute expression (nM) of 17

core apoptosis regulators in a panel of 11 melanoma cell lines, and enriched these data with systems-level information on apoptosis pathway topology. By applying multivariate statistical analysis and multi-dimensional pattern recognition algorithms, the responsiveness of individual cell lines to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or dacarbazine (DTIC) could be predicted with very high accuracy (91 and 82% correct predictions), and the most effective treatment option for individual cell lines could be pre-determined in silico. In contrast, cell death responsiveness was poorly predicted when not taking knowledge on protein-protein interactions into account (55 and 36% correct predictions). We also generated mathematical predictions on whether anti-apoptotic Bcl-2 family members or x-linked inhibitor of apoptosis protein (XIAP) can be targeted to enhance TRAIL responsiveness in individual cell lines. Subsequent experiments, making use of pharmacological Bcl-2/Bcl-xL inhibition or siRNA-based XIAP depletion, confirmed the accuracy of these predictions. We therefore demonstrate that cell death responsiveness to TRAIL or DTIC can be predicted reliably in a large number of melanoma cell lines when investigating expression patterns of apoptosis regulators in the context of their network-level interplay. The capacity to predict responsiveness at the cellular level may contribute to personalizing anti-cancer treatments in the future. Cell Death and Differentiation advance online publication, 9 August 2013; doi:10.1038/cdd.2013.106.

[95]

TÍTULO / TITLE: - Expression of Leukotriene B4 Receptor-1 on CD8+ T Cells Is Required for Their Migration into Tumors To Elicit Effective Antitumor Immunity.

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

REVISTA / JOURNAL: - J Immunol. 2013 Sep 15;191(6):3462-70. doi: 10.4049/jimmunol.1300967. Epub 2013 Aug 19.

●● Enlace al texto completo (gratis o de pago) [4049/jimmunol.1300967](#)

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INSTITUCIÓN / INSTITUTION: - James Graham Brown Cancer Center, University of Louisville Health Sciences, Louisville, KY 40202;

RESUMEN / SUMMARY: - Leukotriene B4 (LTB4) receptor (BLT)1 is expressed on variety of immune cells and has been implicated as a mediator of diverse inflammatory diseases. However, whether biological responses initiated via this receptor generate tumor-promoting inflammation or antitumor immunity remains unexplored. In this study, we investigated the role of BLT1 in antitumor immunity using syngeneic TC-1 cervical cancer model, and observed accelerated tumor growth and reduced survival in BLT1(-/-) mice compared with BLT1(+/+) mice. Analysis of the tumor infiltrates by flow cytometry and confocal microscopy revealed a significant decrease in effector immune cells, most notably, CD8(+) T cells and NK cells in the tumors of the BLT1(-/-) mice. Gene expression profiling confirmed the dramatic decrease of IFN-gamma, granzyme

B, and IL-2 in tumors growing in BLT1(-/-) mice. Furthermore, depletion of CD8(+) T cells enhanced the tumor growth in BLT1(+/+) but not in BLT1(-/-) mice. However, similar levels of Ag-dependent CD8(+) T cell-mediated killing activity were observed in spleens of BLT1(+/+) and BLT1(-/-) mice. Adoptive transfer of CD8(+) T cells from tumor-bearing BLT1(+/+) but not BLT1(-/-) mice significantly reduced tumor growth and increased the survival of Rag2(-/-) mice. Although the homeostatic proliferation and expression profiles of other chemokine receptors of adoptively transferred BLT1(+/+) and BLT1(-/-) CD8(+) T cells appears to be similar, BLT1(+/+) T lymphocytes entered the tumors in greater numbers. These results suggest that BLT1 expression on CD8(+) T cells plays an important role in their trafficking to tumors.

[96]

TÍTULO / TITLE: - Notch-induced transcription factors are predictive of survival and 5-fluorouracil response in colorectal cancer patients.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 20;109(4):1023-30. doi: 10.1038/bjc.2013.431. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.431](#)

AUTORES / AUTHORS: - Candy PA; Phillips MR; Redfern AD; Colley SM; Davidson JA; Stuart LM; Wood BA; Zeps N; Leedman PJ

INSTITUCIÓN / INSTITUTION: - 1] Laboratory for Cancer Medicine, University of Western Australia Centre for Medical Research, Western Australian Institute for Medical Research (WAIMR), Perth, Western Australia 6000, Australia [2] School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009, Australia.

RESUMEN / SUMMARY: - Background: The purpose of this study was to evaluate the expression of Notch-induced transcription factors (NTFs) HEY1, HES1 and SOX9 in colorectal cancer (CRC) patients to determine their clinicopathologic and prognostic significance. Methods: Levels of HEY1, HES1 and SOX9 protein were measured by immunohistochemistry in a nonmalignant and malignant tissue microarray of 441 CRC patients, and the findings correlated with pathologic, molecular and clinical variables. Results: The NTFs HEY1, HES1 and SOX9 were overexpressed in tumours relative to colonic mucosa (OR=3.44, P<0.0001; OR=7.40, P<0.0001; OR=4.08 P<0.0001, respectively). HEY1 overexpression was a negative prognostic factor for all CRC patients (HR=1.29, P=0.023) and strongly correlated with perineural and vascular invasion and lymph node (LN) metastasis. In 5-fluorouracil (5-FU)-treated patients, the tumour overexpression of SOX9 correlated with markedly poorer survival (HR=8.72, P=0.034), but had no predictive effect in untreated patients (HR=0.70, P=0.29). When HEY1, HES1 and SOX9 expression were combined to predict survival with chemotherapy, in treated patients there was an additive increase in the risk of death

with each NTF overexpressed (HR=2.09, P=0.01), but no prognostic import in the untreated patient group (HR=0.74, P=0.19). Conclusion: The present study is the first to discover that HEY1 overexpression correlates with poorer outcome in CRC, and NTF expression is predictive of CRC patient survival with 5-FU chemotherapy. If confirmed in future studies, testing of NTF expression has the potential to enter routine pathological practice for the selection of patients to undergo chemotherapy alone or in combination with Notch inhibitors.

[97]

TÍTULO / TITLE: - Expression of Aryl Hydrocarbon Receptor Nuclear Translocator Enhances Cisplatin Resistance by Upregulating MDR1 Expression in Cancer Cells.

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

REVISTA / JOURNAL: - Mol Pharmacol. 2013 Oct;84(4):591-602. Epub 2013 Aug 1.

●● [Enlace al texto completo \(gratis o de pago\) 1124/mol.113.087197](#)

AUTORES / AUTHORS: - Chan YY; Kalpana S; Chang WC; Chang WC; Chen BK

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, College of Medicine, National Cheng Kung University, Tainan, Taiwan (Y.-Y.C., S.K., B.-K.C.); Department of Clinical Pharmacology and Master Program for Clinical Pharmacogenomics and Pharmacoproteomics, School of Pharmacology, Taipei Medical University, Taipei, Taiwan (W.-Chi.C.); Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan (W.-Cha.C.); Department of Pharmacy, Taipei Medical University-Wanfang Hospital, Taipei, Taiwan (W.-Chi.C.); and Institute of Bioinformatics and Biosignal Transduction, College of Bioscience and Biotechnology, National Cheng Kung University, Tainan, Taiwan (B.-K.C.).

RESUMEN / SUMMARY: - The identification of molecular pathways in cancer cells is important for understanding the cells' underlying biology and for designing effective cancer therapies. We demonstrate that the expression of aryl hydrocarbon receptor nuclear translocator (ARNT) is critical during the development of cisplatin resistance. The reduced expression of ARNT was correlated with cisplatin-induced cell death in drug-sensitive cells. In addition, suppression of ARNT reversed the characteristics of cisplatin-resistant cells, making these cells cisplatin-sensitive, and significantly enhanced caspase-3 activation, DNA fragmentation, and apoptosis. The inhibition of colony formation, regulated by cisplatin, was more significant in ARNT-knockdown cells than in parental cells. In a xenograft analysis of severe combined immunodeficiency mice, cisplatin also efficiently inhibited ARNT-deficient c4 tumors but not ARNT-containing vT2 tumor formation. Furthermore, the downregulation of multidrug resistance 1 (MDR1) expression and retention of drugs in cells caused by suppression of ARNT, resulting in the resensitization of drug-resistant cells to cisplatin, was observed. When overexpressed, ARNT interacted with Sp1 to enhance the expression of MDR1 through Sp1-binding sites on the MDR1 promoter, resulting in a

reversal of the effect of cisplatin on cell death. In addition, ARNT-induced MDR1 expression was inhibited in Sp1-knockdown cells. These results reveal previously unrecognized, multifaceted functions of ARNT in establishing the drug-resistant properties of cancer cells by the upregulation of MDR1, highlighting ARNT's potential as a therapeutic target in an important subset of cancers.

[98]

TÍTULO / TITLE: - High plasma fibrinogen level represents an independent negative prognostic factor regarding cancer-specific, metastasis-free, as well as overall survival in a European cohort of non-metastatic renal cell carcinoma patients.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1123-9. doi: 10.1038/bjc.2013.443. Epub 2013 Aug 6.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.443](#)

AUTORES / AUTHORS: - Pichler M; Hutterer GC; Stojakovic T; Mannweiler S; Pummer K; Zigeuner R

INSTITUCIÓN / INSTITUTION: - Division of Oncology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 25, Graz A=8036, Austria.

RESUMEN / SUMMARY: - Background: In recent years, plasma fibrinogen has been ascribed an important role in the pathophysiology of tumour cell invasion and metastases. A relatively small-scale study has indicated that plasma fibrinogen levels may serve as a prognostic factor for predicting clinical outcomes in non-metastatic renal cell carcinoma (RCC) patients. Methods: Data from 994 consecutive non-metastatic RCC patients, operated between 2000 and 2010 at a single, tertiary academic centre, were evaluated. Analyses of plasma fibrinogen levels were performed one day before the surgical interventions. Patients were categorised using a cut-off value of 466 mg dl(-1) according to a calculation by receiver-operating curve analysis. Cancer-specific (CSS), metastasis-free (MFS), as well as overall survival (OS) were assessed using the Kaplan-Meier method. To evaluate the independent prognostic impact of plasma fibrinogen level, a multivariable Cox regression model was performed for all three different endpoints. Results: High plasma fibrinogen levels were associated with various well-established prognostic factors, including age, advanced tumour stage, tumour grade and histologic tumour necrosis (all P<0.05). Furthermore, in multivariable analysis, a high plasma fibrinogen level was statistically significantly associated with a poor outcome for patients' CSS (hazard ratio (HR): 2.47, 95% confidence interval (CI): 1.49-4.11, P<0.001), MFS (HR: 2.15, 95% CI: 1.44-3.22, P<0.001) and OS (HR: 2.48, 95% CI: 1.80-3.40, P<0.001). Conclusion: A high plasma fibrinogen level seems to represent a strong and independent negative prognostic factor regarding CSS, MFS and OS in non-metastatic RCC patients. Thus, this easily

determinable laboratory value should be considered as an additional prognostic factor for RCC patients' individual risk assessment.

[99]

TÍTULO / TITLE: - Role of Focal Adhesion Kinase in Regulating YB-1-Mediated Paclitaxel Resistance in Ovarian Cancer.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Oct 2;105(19):1485-1495. Epub 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt210](#)

AUTORES / AUTHORS: - Kang Y; Hu W; Ivan C; Dalton HJ; Miyake T; Pecot CV; Zand B; Liu T; Huang J; Jennings NB; Rupaimoole R; Taylor M; Pradeep S; Wu SY; Lu C; Wen Y; Huang J; Liu J; Sood AK

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RESUMEN / SUMMARY: - BACKGROUND: We previously found focal adhesion kinase (FAK) inhibition sensitizes ovarian cancer to taxanes; however, the mechanisms are not well understood. METHODS: We characterized the biologic response of taxane-resistant and taxane-sensitive ovarian cancer models to a novel FAK inhibitor (VS-6063). We used reverse-phase protein arrays (RPPA) to identify novel downstream targets in taxane-resistant cell lines. Furthermore, we correlated clinical and pathological data with nuclear and cytoplasmic expression of FAK and YB-1 in 105 ovarian cancer samples. Statistical tests were two-sided, and P values were calculated with Student t test or Fisher exact test. RESULTS: We found that VS-6063 inhibited FAK phosphorylation at the Tyr397 site in a time- and dose-dependent manner. The combination of VS-6063 and paclitaxel markedly decreased proliferation and increased apoptosis, which resulted in 92.7% to 97.9% reductions in tumor weight. RPPA data showed that VS-6063 reduced levels of AKT and YB-1 in taxane-resistant cell lines. FAK inhibition enhanced chemosensitivity in taxane-resistant cells by decreasing YB-1 phosphorylation and subsequently CD44 in an AKT-dependent manner. In human ovarian cancer samples, nuclear FAK expression was associated with increased nuclear YB-1 expression ($\chi^2 = 37.7$; $P < .001$). Coexpression of nuclear FAK and YB-1 was associated with statistically significantly worse median overall survival (24.9 vs 67.3

months; hazard ratio = 2.64; 95% confidence interval = 1.38 to 5.05; P = .006).

CONCLUSIONS: We have identified a novel pathway whereby FAK inhibition with VS-6063 overcomes YB-1-mediated paclitaxel resistance by an AKT-dependent pathway. These findings have implications for clinical trials aimed at targeting FAK.

[100]

TÍTULO / TITLE: - Correlation between Preferentially Expressed Antigen of Melanoma and Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand Gene Expression in Different Types of Leukaemia Patients.

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

REVISTA / JOURNAL: - Acta Haematol. 2013 Aug 31;130(4):297-304.

●● Enlace al texto completo (gratis o de pago) [1159/000351166](#)

AUTORES / AUTHORS: - Zhang W; Chi K; Zhang Y; Ma B; Shi J; Chen Y; Lei P; Li Y; Sun K

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Henan Provincial Hospital, Zhengzhou University, Zhengzhou, PR China.

RESUMEN / SUMMARY: - Introduction: Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) down-regulation by preferentially expressed antigen of melanoma (PRAME) is a general phenomenon in different types of solid tumours, but research on the correlation between PRAME and TRAIL gene expression in leukaemia patients is rare. Method: PRAME and TRAIL expression was detected in bone marrow samples from 80 newly diagnosed acute leukaemia (AL) patients and 40 chronic myeloid leukaemia (CML) patients using TaqMan-based real-time quantitative PCR methods, and a linear correlation analysis was performed on their levels of expression. A total of 15 normal bone marrow samples from individuals with non-malignant haematological diseases served as normal controls. Results: PRAME expression was higher in both AL and CML patients compared to controls (both $p < 0.001$). CML patients in both blast crisis (BC) and the accelerated phase (AP) had significantly higher PRAME levels than CML patients in the chronic phase (CP) ($p = 0.006$ and 0.0461 , respectively). TRAIL expression was higher in both the acute myeloid leukaemia (AML) group and the acute lymphoblastic leukaemia (ALL) group than in the controls ($p = 0.039$ and 0.047 , respectively). In contrast, CML patients had lower TRAIL levels than controls ($p = 0.043$), and TRAIL expression in CML patients in the advanced phases (BC and AP) was significantly lower than in CML-CP patients ($p = 0.006$). In CML patients, there was a significant inverse correlation (Spearman's $R = -0.6669$, $p < 0.0001$) between PRAME and TRAIL gene expression, while a greater significant inverse correlation was found in patients in the advanced phases (BC and AP) ($R = -0.6764$). In addition, no correlation was observed in AML and ALL patients. Conclusion: The simultaneous detection of PRAME and TRAIL gene expression may be helpful to monitor condition changes in leukaemia patients and evaluate therapeutic effects in clinical practice, particularly in CML patients. © 2013 S. Karger AG, Basel.

[101]

TÍTULO / TITLE: - Phase I clinical and pharmacokinetic/pharmacogenetic study of a triplet regimen of S-1/irinotecan/oxaliplatin in patients with metastatic colorectal or gastric cancer.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2272-0](#)

AUTORES / AUTHORS: - Park SR; Hong YS; Lim HS; Seong MW; Kong SY; Kim SY; Park YI; Jung KH

INSTITUCIÓN / INSTITUTION: - Center for Gastric Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea.

RESUMEN / SUMMARY: - PURPOSE: We conducted a phase I study of S-1 combined with irinotecan and oxaliplatin (TIROX) to determine the maximum-tolerated dose (MTD) and recommended dose (RD) and to assess its safety, pharmacokinetics, pharmacogenetics, and preliminary efficacy in patients with metastatic colorectal cancer (MCRC) or metastatic gastric cancer (MGC). METHODS: Patients received escalating doses of S-1 (30-40 mg/m² b.i.d.) orally on days 1-14, an escalating dose of intravenous irinotecan (120-150 mg/m²) on day 1, and a fixed dose of intravenous oxaliplatin (85 mg/m²) on day 1 every 3 weeks. RESULTS: Twenty-three patients (10 MCRC, 13 MGC; 13 chemo-naïve, 10 previously treated for metastatic disease) were treated across six dose levels. Because only one patient experienced a dose-limiting toxicity of grade 3 anorexia at the highest dose level (S-1 40 mg/m² b.i.d., irinotecan 150 mg/m², and oxaliplatin 85 mg/m²) (n = 8), the MTD was not obtained, and this level was established as the RD. With a median of 10 cycles per patient, the most common grade 3 or 4 adverse events included neutropenia (43 %), diarrhea (13 %), and nausea (13 %). In 22 efficacy-evaluable patients, the objective tumor response rate was 59.1 % (75 % for both MCRC and MGC in the first-line setting) and the disease control rate was 100 %. The exploratory pharmacokinetic/pharmacogenetic study showed that CYP2A6 variants (*4, *7, *9) are associated with a lower metabolic ratio of S-1 (exposure ratio of 5-fluorouracil to tegafur). CONCLUSIONS: The new triplet TIROX regimen has shown promising antitumor activity and a favorable toxicity profile in patients with MCRC and MGC.

[102]

TÍTULO / TITLE: - Safety and efficacy of a genetic vaccine targeting telomerase plus chemotherapy for the therapy of canine B-cell lymphoma.

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

REVISTA / JOURNAL: - Hum Gene Ther. 2013 Aug;24(8):728-38. doi: 10.1089/hum.2013.112.

●● Enlace al texto completo (gratis o de pago) [1089/hum.2013.112](https://doi.org/10.1089/hum.2013.112)

AUTORES / AUTHORS: - Gavazza A; Lubas G; Fridman A; Peruzzi D; Impellizeri JA; Luberto L; Marra E; Roscilli G; Ciliberto G; Aurisicchio L

INSTITUCIÓN / INSTITUTION: - 1 University of Pisa , Department of Veterinary Sciences, San Piero a Grado 56122, Pisa, Italy .

RESUMEN / SUMMARY: - Abstract Client-owned pet dogs represent exceptional translational models for advancement of cancer research because they reflect the complex heterogeneity observed in human cancer. We have recently shown that a genetic vaccine targeting dog telomerase reverse transcriptase (dTERT) and based on adenovirus DNA electro-gene-transfer (Ad/DNA-EGT) technology can induce strong cell-mediated immune responses against this tumor antigen and increase overall survival of dogs affected by B-cell lymphosarcoma (LSA) in comparison with historical controls when combined with a cyclophosphamide, vincristine, and prednisone (COP) chemotherapy regimen. Here, we have conducted a double-arm clinical trial with an extended number of LSA patients, measured the antigen-specific immune response, and evaluated potential toxic effects of the immunotherapy along with a follow-up of patients survival for 3.5 years. The immune response was measured by enzyme-linked immunospot assay. The expression of dTERT was quantified by quantitative polymerase chain reaction. Changes in hematological parameters, local/systemic toxicity or organic dysfunction and fever were monitored over time during the treatment. dTERT-specific cell-mediated immune responses were induced in almost all treated animals. No adverse effects were observed in any dog patient that underwent treatment. The overall survival time of vaccine/COP-treated dogs was significantly increased over the COP-only cohort (>76.1 vs. 29.3 weeks, respectively, $p < 0.0001$). There was a significant association between dTERT expression levels in LSA cells and overall survival among vaccinated patients. In conclusion, Ad/DNA-EGT-based cancer vaccine against dTERT in combination with COP chemotherapy is safe and significantly prolongs the survival of LSA canine patients. These data confirm the therapeutic efficacy of dTERT vaccine and support the evaluation of this approach for other cancer types as well as the translation of this approach to human clinical trials.

[103]

TÍTULO / TITLE: - DNA methylation signatures for prediction of biochemical recurrence after radical prostatectomy of clinically localized prostate cancer.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 10;31(26):3250-8. doi: 10.1200/JCO.2012.47.1847. Epub 2013 Aug 5.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.47.1847](https://doi.org/10.1200/JCO.2012.47.1847)

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INSTITUCIÓN / INSTITUTION: - Christa Haldrup, Kamilla Mundbjerg, Else Marie Vestergaard, Philippe Lamy, Michael Borre, Soren Hoyer, Torben F. Orntoft, and Karina D. Sorensen, Aarhus University Hospital, Aarhus, Denmark; Peter Wild, University Hospital Zurich, Zurich, Switzerland; Wolfgang A. Schulz and Christian Arsov, Heinrich Heine University, Dusseldorf, Germany; and Tapio Visakorpi, University of Tampere and Tampere University Hospital, Tampere, Finland.

RESUMEN / SUMMARY: - PURPOSE: Diagnostic and prognostic tools for prostate cancer (PC) are suboptimal, causing overtreatment of indolent PC and risk of delayed treatment of aggressive PC. Here, we identify six novel candidate DNA methylation markers for PC with promising diagnostic and prognostic potential. METHODS: Microarray-based screening and bisulfite sequencing of 20 nonmalignant and 29 PC tissue specimens were used to identify new candidate DNA hypermethylation markers for PC. Diagnostic and prognostic potential was evaluated in 35 nonmalignant prostate tissue samples, 293 radical prostatectomy (RP) samples (cohort 1, training), and 114 malignant RP samples (cohort 2, validation) collected in Denmark, Switzerland, Germany, and Finland. Sensitivity and specificity for PC were evaluated by receiver operating characteristic analyses. Correlations between DNA methylation levels and biochemical recurrence were assessed using log-rank tests and univariate and multivariate Cox regression analyses. RESULTS: Hypermethylation of AOX1, C1orf114, GAS6, HAPLN3, KLF8, and MOB3B was highly cancer specific (area under the curve, 0.89 to 0.98). Furthermore, high C1orf114 methylation was significantly ($P < .05$) associated with biochemical recurrence in multivariate analysis in cohort 1 (hazard ratio [HR], 3.10; 95% CI, 1.89 to 5.09) and was successfully validated in cohort 2 (HR, 3.27; 95% CI, 1.17 to 9.12). Moreover, a significant ($P < .05$) three-gene prognostic methylation signature (AOX1/C1orf114/HAPLN3), classifying patients into low- and high-methylation subgroups, was trained in cohort 1 (HR, 1.91; 95% CI, 1.26 to 2.90) and validated in cohort 2 (HR, 2.33; 95% CI, 1.31 to 4.13). CONCLUSION: We identified six novel candidate DNA methylation markers for PC. C1orf114 hypermethylation and a three-gene methylation signature were independent predictors of time to biochemical recurrence after RP in two PC patient cohorts.

[104]

TÍTULO / TITLE: - Inflammation-related DNA damage and expression of CD133 and Oct3/4 in cholangiocarcinoma patients with poor prognosis.

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

REVISTA / JOURNAL: - Free Radic Biol Med. 2013 Jul 31. pii: S0891-5849(13)00378-X. doi: 10.1016/j.freeradbiomed.2013.07.034.

- Enlace al texto completo (gratis o de pago)

[1016/j.freeradbiomed.2013.07.034](https://doi.org/10.1016/j.freeradbiomed.2013.07.034)

AUTORES / AUTHORS: - Thanan R; Pairojkul C; Pinlaor S; Khuntikeo N; Wongkham C; Sripa B; Ma N; Vaeteewoottacharn K; Furukawa A; Kobayashi H; Hiraku Y; Oikawa S; Kawanishi S; Yongvanit P; Murata M

RESUMEN / SUMMARY: - Nitrate and oxidative DNA damage plays an important role in inflammation-related carcinogenesis. Chronic inflammation such as parasite infection and primary sclerosing cholangitis can be an etiological factor of cholangiocarcinoma. Using a proteomic approach and double-fluorescent staining, we identified high expression and colocalization of albumin and cytokeratin-19 in liver fluke-associated cholangiocarcinoma tissues, compared with normal livers from cholangiocarcinoma patients and cadaveric donors, respectively. Albumin was detected not only in cells of hyperplastic bile ducts and cholangiocarcinoma, but also in liver stem/progenitor cell origin, such as canal of Hering, ductules, and ductular reactions, suggesting the involvement of stem/progenitor cells in cholangiocarcinoma development. To clarify the involvement of liver stem/progenitor cells in cholangiocarcinoma, we examined several stem/progenitor cell markers (CD133, CD44, OV6, and Oct3/4) in cholangiocarcinoma tissues analyzed by immunohistochemical staining, and measured 8-oxodG levels by using HPLC-ECD as an inflammation-related DNA lesion. In addition, a stem/progenitor cell factor Bmi1, 8-nitroguanine (formed during nitrate DNA damage), DNA damage response (DDR) proteins (phosphorylated ATM and gamma-H2AX), and manganese-SOD (Mn-SOD) were analyzed by immunohistochemistry. Stem/progenitor cell markers (CD133, OV6, CD44, and Oct3/4) were positively stained in 56, 38, 47, and 56% of 34 cholangiocarcinoma cases, respectively. Quantitative analysis of 8-oxodG revealed significantly increased levels in CD133- and/or Oct3/4-positive tumor tissues compared to negative tumor tissues, as well as 8-nitroguanine formation detected by immunohistochemistry. In the cases of CD44- and/or OV6-positive tissue, no significant difference was observed. Cholangiocarcinoma patients with CD133- and/or Oct3/4-positive tumor tissues showed significantly lower expression of Mn-SOD and higher DDR protein, gamma-H2AX. Moreover, CD133- and/or Oct3/4-positive cholangiocarcinoma patients had significant associations with tumor histology types, tumor stage, and poor prognoses. Our results suggest that CD133 and Oct3/4 in cholangiocarcinoma are associated with increased formation of DNA lesions and the DDR protein, which may be involved in genetic instability and lead to cholangiocarcinoma development with aggressive clinical features.

[105]

TÍTULO / TITLE: - Anticancer effects of the engineered stem cells transduced with therapeutic genes via a selective tumor tropism caused by vascular endothelial growth factor toward HeLa cervical cancer cells.

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

REVISTA / JOURNAL: - Mol Cells. 2013 Sep 2.

●● Enlace al texto completo (gratis o de pago) [1007/s10059-013-0153-3](#)

AUTORES / AUTHORS: - Kim HS; Yi BR; Hwang KA; Kim SU; Choi KC

INSTITUCIÓN / INSTITUTION: - Laboratory of Veterinary Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, 361-763, Korea.

RESUMEN / SUMMARY: - The aim of the present study was to investigate the therapeutic efficacy of genetically engineered stem cells (GESTECs) expressing bacterial cytosine deaminase (CD) and/ or human interferon-beta (IFN-beta) gene against HeLa cervical cancer and the migration factors of the GESTECs toward the cancer cells. Anticancer effect of GESTECs was examined in a co-culture with HeLa cells using MTT assay to measure cell viability. A transwell migration assay was performed so as to assess the migration capability of the stem cells to cervical cancer cells. Next, several chemoattractant ligands and their receptors related to a selective migration of the stem cells toward HeLa cells were determined by real-time PCR. The cell viability of HeLa cells was decreased in response to 5-fluorocytosine (5-FC), a prodrug, indicating that 5-fluorouracil (5-FU), a toxic metabolite, was converted from 5-FC by CD gene and it caused the cell death in a co-culture system. When IFN-beta was additionally expressed with CD gene by these GESTECs, the anticancer activity was significantly increased. In the migration assay, the GESTECs selectively migrated to HeLa cervical cancer cells. As results of real-time PCR, chemoattractant ligands such as MCP-1, SCF, and VEGF were expressed in HeLa cells, and several receptors such as uPAR, VEGFR2, and c-kit were produced by the GESTECs. These GESTECs transduced with CD gene and IFN-beta may provide a potential of a novel gene therapy for anticervical cancer treatments via their selective tumor tropism derived from VEGF and VEGFR2 expressions between HeLa cells and the GESTECs.

[106]

TÍTULO / TITLE: - Evaluation of PIK3CA Mutation As a Predictor of Benefit From Nonsteroidal Anti-Inflammatory Drug Therapy in Colorectal Cancer.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2013.50.0322](#)

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INSTITUCIÓN / INSTITUTION: - Enric Domingo, David N. Church, Rajarajan Ramamoorthy, and Ian P.M. Tomlinson, The Wellcome Trust Centre for Human Genetics, University of Oxford; David N. Church, David J. Kerr, and Rachel Midgley, Oxford Cancer Centre, Churchill Hospital; Yoko Yanagisawa, Elaine Johnstone, David J. Kerr, and Rachel

Midgley, University of Oxford, Oxford; Rajarajan Ramamoorthy and Brian Davidson, University College London, Royal Free Hospital, London, United Kingdom; and Oliver Sieber, Ludwig Colon Cancer Initiative Laboratory, Ludwig Institute for Cancer Research, Melbourne, Victoria, Australia.

RESUMEN / SUMMARY: - PURPOSE: Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) protect against colorectal cancer (CRC) and are associated with reduced disease recurrence and improved outcome after primary treatment. However, toxicities of NSAIDs have limited their use as antineoplastic therapy. Recent data have suggested that the benefit of aspirin after CRC diagnosis is limited to patients with PIK3CA-mutant cancers. We sought to determine the predictive utility of PIK3CA mutation for benefit from both cyclooxygenase-2 inhibition and aspirin. METHODS: We performed molecular analysis of tumors from 896 participants in the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) trial, a large randomized trial comparing rofecoxib with placebo after primary CRC resection. We compared relapse-free survival and overall survival between rofecoxib therapy and placebo and between the use and nonuse of low-dose aspirin, according to tumor PIK3CA mutation status. RESULTS: We found no evidence of a greater benefit from rofecoxib treatment compared with placebo in patients whose tumors had PIK3CA mutations (multivariate adjusted hazard ratio [HR], 1.2; 95% CI, 0.53 to 2.72; $P = .66$; $P_{INTERACTION} = .47$) compared with patients with PIK3CA wild-type cancers (HR, 0.87; 95% CI, 0.64 to 1.16; $P = .34$). In contrast, regular aspirin use after CRC diagnosis was associated with a reduced rate of CRC recurrence in patients with PIK3CA-mutant cancers (HR, 0.11; 95% CI, 0.001 to 0.832; $P = .027$; $P_{INTERACTION} = .024$) but not in patients lacking tumor PIK3CA mutation (HR, 0.92; 95% CI, 0.60 to 1.42; $P = .71$). CONCLUSION: Although tumor PIK3CA mutation does not predict benefit from rofecoxib treatment, it merits further evaluation as a predictive biomarker for aspirin therapy. Our findings are concordant with recent data and support the prospective investigation of adjuvant aspirin in PIK3CA-mutant CRC.

[107]

TÍTULO / TITLE: - Genomic Imbalance Defines Three Prognostic Groups for Risk Stratification of Chronic Lymphocytic Leukemia Patients.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.845882](https://doi.org/10.1007/s10428194.2013.845882)

AUTORES / AUTHORS: - Houldsworth J; Guttapalli A; Thodima V; Yan XJ; Mendiratta G; Zielonka T; Nanjangud G; Chen W; Patil S; Mato A; Brown JR; Rai K; Chiorazzi N; Chaganti RS

RESUMEN / SUMMARY: - ABSTRACT Array comparative genomic hybridization (aCGH) has yet to be fully leveraged in a prognostic setting in chronic lymphocytic leukemia (CLL).

Genomic imbalance was assessed in 288 CLL specimens using a targeted array. Based on 20 aberrations in a hierarchical manner, all 228 treatment-naive specimens were classified into a group with poor outcome (20.6%) exhibiting at least one aberration that univariately associated with adverse outcome (gain: 2p, 3q, 8q, 17q, loss: 7q, 8p, 11q, 17p, 18p), good outcome (32.5%) showing 13q14 loss without any of the other ten aberrations (gain: 1p, 7p, 12, 18p, 18q, 19, loss: 4p, 5p, 6q, 7p), or intermediate outcome (remainder). The three groups significantly separated with respect to time to first treatment and overall survival ($P < 0.001$) and validation of the stratification scheme was performed in two independent datasets. Gain of 3q and 8q, and 17p loss were determined to be independent unfavorable prognostic biomarkers. TP53, NOTCH1, and SF3B1 mutations correlated with the presence of one poor outcome aCGH marker, at a considerably higher frequency than when only considering poor risk aberrations routinely detected by FISH. These data support genomic imbalance evaluation in CLL by aCGH to assist in risk stratification.

[108]

TÍTULO / TITLE: - The combined use of the neutrophil-lymphocyte ratio and C-reactive protein level as prognostic predictors in adult patients with soft tissue sarcoma.

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

REVISTA / JOURNAL: - J Surg Oncol. 2013 Sep 9. doi: 10.1002/jso.23424.

●● [Enlace al texto completo \(gratis o de pago\) 1002/jso.23424](#)

AUTORES / AUTHORS: - Nakamura T; Matsumine A; Matsubara T; Asanuma K; Uchida A; Sudo A

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan.

RESUMEN / SUMMARY: - **BACKGROUND:** The aim of this study was to determine whether the combined use of the C-reactive protein (CRP) level and neutrophil-lymphocyte ratio (NLR) before treatment predicts disease-specific survival in adult patients with soft tissue sarcoma (STS). **METHODS:** We retrospectively reviewed 142 patients who presented with STS between 1995 and 2010. **RESULTS:** The NLR varied from 0.54 to 7.59. An elevated CRP level was observed in 36 patients before treatment. The patients with both an elevated CRP level and high NLR had a poorer disease-specific survival (46% at 5 years) than the patients with both a normal CRP level and low NLR (87% at 5 years) ($P = 0.0005$). The patients with both an elevated CRP level and high NLR also had a poorer disease-specific survival than the patients with either an elevated CRP level or high NLR (75.6% at five years) ($P = 0.03$). There were no significant prognostic differences between the patients with a normal CRP level and low NLR and those with either an elevated CRP level or high NLR ($P = 0.18$). A multivariate analysis also showed the preoperative NLR and CRP level to be independent predictors of survival. **CONCLUSIONS:** We recommend the routine

measurement of these markers to identify patients with a greater risk of death. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

[109]

TÍTULO / TITLE: - Phase I clinical, pharmacokinetic, and pharmacodynamic study of the Akt-inhibitor triciribine phosphate monohydrate in patients with advanced hematologic malignancies.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug 6. pii: S0145-2126(13)00277-4. doi: 10.1016/j.leukres.2013.07.034.

●● Enlace al texto completo (gratis o de pago) 1016/j.leukres.2013.07.034

AUTORES / AUTHORS: - Sampath D; Malik A; Plunkett W; Nowak B; Williams B; Burton M; Verstovsek S; Faderl S; Garcia-Manero G; List AF; Sebt S; Kantarjian HM; Ravandi F; Lancet JE

INSTITUCIÓN / INSTITUTION: - Departments of Experimental Therapeutics, M.D. Anderson Cancer Center, Houston, TX, USA.

RESUMEN / SUMMARY: - Akt, a serine/threonine protein kinase, is constitutively phosphorylated and hyperactivated in multiple cancers, including acute myeloid leukemia. High levels are linked to poor survival and inferior responses to chemotherapy, making Akt inhibition an attractive therapeutic target. In this phase I/II study of TCN-PM, a small-molecule Akt inhibitor, TCN-PM therapy was well tolerated in patients with advanced hematological malignancies, and reduced levels of phosphorylation of Akt and its substrate Bad were shown, consistent with inhibition of this survival pathway and induction of cell death. Further investigation of TCN-PM alone or in combination in patients with high Akt levels is warranted.

[110]

TÍTULO / TITLE: - Predictive and prognostic significance of cytoplasmic expression of ELAV-like protein HuR in invasive breast cancer treated with neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Sep;141(2):213-24. doi: 10.1007/s10549-013-2679-7. Epub 2013 Sep 14.

●● Enlace al texto completo (gratis o de pago) 1007/s10549-013-2679-7

AUTORES / AUTHORS: - Wang J; Li D; Wang B; Wu Y

INSTITUCIÓN / INSTITUTION: - Department of Oncology, General Hospital, Jinan Command of the People's Liberation Army, Jinan, China.

RESUMEN / SUMMARY: - Cytoplasmic HuR is associated with reduced survival in invasive breast cancer. We designed this study to determine the predictive and prognostic

value of HuR expression in women with breast cancer who underwent neoadjuvant chemotherapy followed by surgical resection. We immunohistochemically analyzed cytoplasmic HuR expression in tumor biopsy cores obtained from 139 patients with invasive breast cancers who received paclitaxel and anthracycline-based neoadjuvant chemotherapy. We evaluated the relationship of HuR expression level with pathologic complete response (pCR), local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS), recurrence-free survival (RFS), and overall survival (OS). Cytoplasmic HuR expression was present in 60 cases (43.2 %). The expression of cytoplasmic HuR was significantly associated with high nuclear grade ($P < 0.0001$) and ER ($P = 0.001$) and PR ($P = 0.005$) status. Multivariate regression analysis further revealed that high nuclear grade ($P = 0.023$), negative ER status ($P = 0.043$), and human epidermal growth factor receptor 2 (HER2) overexpression ($P < 0.0001$), but not cytoplasmic HuR expression, were significant independent predictors of pCR. Interestingly, multivariate Cox analysis revealed that cytoplasmic HuR expression was a strong independent predictor of reduced LRFS ($P = 0.014$), DRFS ($P = 0.001$), RFS ($P < 0.0001$), and OS ($P = 0.019$) irrespective of pCR. Furthermore, the patient group with tumors showing both expression of cytoplasmic HuR and non-pCR had a worse prognosis in LRFS ($P = 0.048$), DRFS ($P < 0.0001$), RFS ($P < 0.0001$), and OS ($P = 0.001$) than did other patient groups; patients with tumors showing negative cytoplasmic expression of HuR and pCR had the best prognosis in all RFS and OS. Cytoplasmic expression of HuR is an independent prognostic marker in breast cancer patients undergoing chemotherapy. Combination analyses of HuR expression and pCR, compared with pCR alone, can better predict clinical outcome in patients with primary breast cancer.

[111]

TÍTULO / TITLE: - A four-miRNA signature identified from genome-wide serum miRNA profiling predicts survival in patients with nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Sep 2. doi: 10.1002/ijc.28468.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28468](#)

AUTORES / AUTHORS: - Liu N; Cui RX; Sun Y; Guo R; Mao YP; Tang LL; Jiang W; Liu X; Cheng YK; He QM; Cho WC; Liu LZ; Li L; Ma J

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China.

RESUMEN / SUMMARY: - Recent findings have reported that human serum microRNAs (miRNAs) can be used as prognostic biomarkers in various cancers. We aimed to explore the prognostic value of serum miRNAs in nasopharyngeal carcinoma (NPC) patients. The level of serum miRNA was retrospectively analyzed in 512 NPC patients recruited between January 2001 and December 2006. In the discovery stage, a microarray followed by RT-qPCR was used to identify differentially altered miRNAs in

eight patients with shorter survival and eight patients with longer survival who were well matched by age, sex and clinical stage. The identified serum miRNAs were then validated in all 512 samples, which were randomly divided into a training set and a validation set. Four serum miRNAs (miR-22, miR-572, miR-638 and miR-1234) were found to be differentially altered and were used to construct a miRNA signature. Risk scores were calculated to classify the patients into high- or low-risk groups. Patients with high-risk scores had poorer overall survival (HR, 2.54; 95% CI, 1.57-4.12; $p < 0.001$) and distant-metastasis-free survival (HR, 3.28; 95% CI, 1.82-5.94; $p < 0.001$) than those with low-risk scores in the training set; these results were confirmed in the validation and combined sets. The miRNA signature and TNM stage were independent prognostic factors. The combination of the miRNA signature and TNM stage had a better prognostic value than the TNM stage or miRNA signature alone. The four-serum miRNA signature may add prognostic value to the TNM staging system and provide information for personalized therapy in NPC. © 2013 Wiley Periodicals, Inc.

[112]

TÍTULO / TITLE: - N1-guanyl-1,7-diaminoheptane (GC7) enhances the therapeutic efficacy of doxorubicin by inhibiting activation of eukaryotic translation initiation factor 5^a2 (eIF5A2) and preventing the epithelial-mesenchymal transition in hepatocellular carcinoma cells.

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

REVISTA / JOURNAL: - Exp Cell Res. 2013 Aug 16. pii: S0014-4827(13)00339-X. doi: 10.1016/j.yexcr.2013.08.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexcr.2013.08.010](#)

AUTORES / AUTHORS: - Lou B; Fan J; Wang K; Chen W; Zhou X; Zhang J; Lin S; Lv F; Chen Y
INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China.

RESUMEN / SUMMARY: - Hepatocellular carcinoma (HCC) cells undergo the epithelial-mesenchymal transition (EMT) during chemotherapy, which reduces the efficacy of doxorubicin-based chemotherapy. We investigated N1-guanyl-1,7-diaminoheptane (GC7) which inhibits eukaryotic translation initiation factor 5^a2 (eIF5A2) activation; eIF5A2 is associated with chemoresistance. GC7 enhanced doxorubicin cytotoxicity in epithelial HCC cells (Huh7, Hep3B and HepG2) but had little effect in mesenchymal HCC cells (SNU387, SNU449). GC7 suppressed the doxorubicin-induced EMT in epithelial HCC cells; knockdown of eIF5A2 inhibited the doxorubicin-induced EMT and enhanced doxorubicin cytotoxicity. GC7 combination therapy may enhance the therapeutic efficacy of doxorubicin in HCC by inhibiting eIF5A2 activation and preventing the EMT.

[113]

TÍTULO / TITLE: - REG Ialpha gene expression is linked with the poor prognosis of lung adenocarcinoma and squamous cell carcinoma patients via discrete mechanisms.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Sep 19. doi: 10.3892/or.2013.2739.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2739](#)

AUTORES / AUTHORS: - Kimura M; Naito H; Tojo T; Itaya-Hironaka A; Dohi Y; Yoshimura M; Nakagawara KI; Takasawa S; Taniguchi S

INSTITUCIÓN / INSTITUTION: - Department of Thoracic and Cardiovascular Surgery, Nara Medical University, Kashihara, Nara 634-8522, Japan.

RESUMEN / SUMMARY: - The aim of the present study was to evaluate the effects of the REG Ialpha and REG Ibeta genes on lung cancer cell lines, and thereafter, the expression of REG family genes (REG Ialpha, REG Ibeta, REG III, HIP/PAP and REG IV) in lung cancer in relation to patient prognosis was evaluated. Lung adenocarcinoma (AD) and squamous cell carcinoma (SCC) cell lines expressing REG Ialpha or REG Ibeta (HLC-1 REG Ialpha/Ibeta and EBC-1 REG Ialpha/Ibeta) were established, and cell number, cell invasive activity, and anchorage-independent cell growth were compared with these variables in the control cells. The expression levels of REG family genes were evaluated by real-time RT-PCR in surgically resected lung cancers, and disease-specific survival (DSS) curves were generated. The HLC-1 REG Ialpha/Ibeta cell line showed significant increases in cell number and anchorage-independent cell growth compared with the control cells. EBC-1 REG Ialpha/Ibeta cells showed significant increases in cell invasive activity and anchorage-independent cell growth as compared with the control cells. Except for the REG Ibeta gene, expression of other REG family genes was observed in the surgically resected samples; however, DSS was significantly worse only in stage I patients who were positive for REG Ialpha expression than in patients who were negative for REG Ialpha expression. The effects of REG Ialpha on AD and SCC cells were different in the in vitro study, and a correlation between REG Ialpha expression and patient prognosis was noted in the in vivo study. Therefore, overexpression of REG Ialpha is a risk factor for poor prognosis caused by discrete mechanisms in AD and SCC patients.

[114]

TÍTULO / TITLE: - Prognostic value of EpCAM/MUC1 mRNA-positive cells in non-small cell lung cancer patients.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 7.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1162-8](#)

AUTORES / AUTHORS: - Zhu WF; Li J; Yu LC; Wu Y; Tang XP; Hu YM; Chen YC

INSTITUCIÓN / INSTITUTION: - Department of Pulmonary Medicine, Affiliated Hospital of Jiangsu University, No. 438 North Jiefang Street, Zhenjiang, China.

RESUMEN / SUMMARY: - The aim of this study was to assess the prognostic value of EpCAM/MUC1 mRNA-positive circulating tumor cells (CTCs) in patients with non-small cell lung cancer (NSCLC). The presence of EpCAM/MUC1 mRNA-positive CTCs was evaluated in 74 NSCLC patients before the initiation of any therapy, from which 61 patients with surgical resection of tumor were also evaluable for EpCAM/MUC1 mRNA-positive CTC analysis after surgery, by quantitative real-time PCR assay. Sixty patients with benign lung disease (BLD) entered this study as controls. The results showed that blood levels of EpCAM and MUC1 mRNA in NSCLC patients before and after surgery were significantly higher than those in BLD patients ($P = 0.001$ and $P = 0.015$, respectively, for EpCAM; $P = 0.003$ and $P = 0.026$, respectively, for MUC1), and the levels of the two gene mRNA in NSCLC patients significantly decreased after surgery ($P = 0.025$ and $P = 0.033$, respectively). Disease recurrence significantly increased in NSCLC patients with EpCAM/MUC1 mRNA-positive CTC preoperation and postoperation ($P = 0.004$ and $P = 0.001$, respectively). Disease-free survival and overall survival significantly reduced in patients with EpCAM/MUC1 mRNA-positive CTC preoperation and postoperation ($P = 0.012$ and $P = 0.002$, respectively, for preoperation; both $P < 0.001$ for postoperation). Multivariate analysis demonstrated that the presence of EpCAM/MUC1 mRNA-positive CTCs before and after surgery was an independent factor associated with disease recurrence. In conclusion, the detection of EpCAM/MUC1 mRNA-positive CTCs in the blood before and after surgery is useful for predicting a poor prognosis in NSCLC patients who undergo curative surgery.

[115]

TÍTULO / TITLE: - Expression status of wild-type HSP110 correlates with HSP110 T deletion size and patient prognosis in microsatellite-unstable colorectal cancer.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Sep 13. doi: 10.1038/modpathol.2013.160.

●● Enlace al texto completo (gratis o de pago) [1038/modpathol.2013.160](#)

AUTORES / AUTHORS: - Kim JH; Kim KJ; Rhee YY; Oh S; Cho NY; Lee HS; Kang GH

INSTITUCIÓN / INSTITUTION: - 1] Department of Pathology, Seoul National University College of Medicine, Seoul, South Korea [2] Department of Pathology, SMG-SNU Boramae Medical Center, Seoul, South Korea.

RESUMEN / SUMMARY: - It has been recently suggested that the expression levels of mutant HSP110 could be a prognostic marker in colorectal cancer with a high level of microsatellite instability (MSI-H). The aim of our study was to validate the prognostic significance of HSP110 mutation using immunohistochemistry and DNA testing in MSI-H colorectal cancer. Wild-type HSP110 (HSP110wt)-specific immunohistochemistry was performed in 168 MSI-H colorectal cancer tissues, and their expression levels were evaluated using a four-tier scoring system (0/1+/2+/3+). Of these tissues, 167 cases were analyzed for HSP110 T17 deletion. Associations with clinicopathological,

molecular and survival parameters were statistically analyzed. The low-level expression of HSP110wt (0/1+) was observed in 40 MSI-H colorectal cancers (24%) and was significantly related to large HSP110 T17 deletions (≥ 4 bp, $P < 0.001$). In survival analysis, patients with low HSP110wt expression (0/1+) showed better disease-free survival compared with those with high expression (2+/3+; $P = 0.005$). This significance in survival difference was maintained in patients with 5-fluorouracil-based chemotherapy-treated tumors ($P = 0.024$) and in those with stage III/IV tumors ($P = 0.032$). Multivariate analysis confirmed the role of HSP110wt expression as an independent prognostic factor ($P = 0.016$, hazard ratio=4.32). In MSI-H colorectal cancer, a low expression of HSP110wt is associated with large HSP110 T17 deletions and better clinical outcome. Immunohistochemistry of HSP110wt can be a simple and valuable tool for the prognostic and therapeutic stratification of patients with MSI-H colorectal cancer. Modern Pathology advance online publication, 13 September 2013; doi:10.1038/modpathol.2013.160.

[116]

TÍTULO / TITLE: - Chemokine receptor CCR7 expression predicts poor outcome in uveal melanoma and relates to liver metastasis whereas expression of CXCR4 is not of clinical relevance.

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

REVISTA / JOURNAL: - Invest Ophthalmol Vis Sci. 2013 Sep 19. pii: iovs.13-12407v1. doi: 10.1167/iov.13-12407.

●● Enlace al texto completo (gratis o de pago) [1167/iov.13-12407](#)

AUTORES / AUTHORS: - van den Bosch T; Koopmans AE; Vaarwater J; van den Berg M; De Klein A; Verdijk RM

INSTITUCIÓN / INSTITUTION: - Pathology, Erasmus University Medical Center, Dr. Molewaterplein 50, Rotterdam, Zuid-Holland, 3015 GE, Netherlands.

RESUMEN / SUMMARY: - Purpose: To examine the prognostic relevance of expression of the chemokine receptors CCR7 and CXCR4 and its ligand CXCL12 in uveal melanoma in non-metastatic and metastatic patients with correlation to liver metastasis and overall survival. Methods: -Primary uveal melanoma specimens from 19 patients with correlating liver metastasis specimens and 30 primary uveal melanoma specimens of patients without metastasis were collected between the years 1988-2008. Expression of CCR7, CXCR4 and CXCL12 was studied using immunohistochemistry. Single nucleotide polymorphism (SNP) arrays were used to examine gains or losses of chromosomes 1, 3, 6 and 8 and the regions of CCR7 (17q12-q21.2), CXCR4 (2q21) and CXCL12 (10q11.1) genes. Results: -Strong cytoplasmic staining for CCR7 correlated with the presence of epithelioid cells ($p = 0.037$), tumor thickness ($p = 0.011$), lymphocytic infiltration ($p = 0.041$) and necrosis ($p = 0.045$). Nuclear staining for CXCR4 correlated with lymphocytic infiltration ($p = 0.017$). CXCL12 showed no correlation to histological

parameters. SNP analyses showed no copy number variations in the regions of CCR7, CXCR4 or CXCL12. Strong expression of CCR7 was observed in 76% of the metastatic patients and 0% of non-metastasis patients. In multivariate analysis, CCR7 staining was inversely correlated to overall survival and disease-free survival whereas CXCR4 nuclear staining was not. Conclusions: -Our data suggest that CCR7 plays a role in uveal melanoma metastasis and is associated with poor survival. CCR7 and its involved related pathways are of prognostic value in uveal melanoma and may prove to be a target for therapeutic intervention.

[117]

TÍTULO / TITLE: - Denosumab and Bone Metastasis-Free Survival in Men With Nonmetastatic Castration-Resistant Prostate Cancer: Exploratory Analyses by Baseline Prostate-Specific Antigen Doubling Time.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.44.6716](#)

AUTORES / AUTHORS: - Smith MR; Saad F; Oudard S; Shore N; Fizazi K; Sieber P; Tombal B; Damiao R; Marx G; Miller K; Van Veldhuizen P; Morote J; Ye Z; Dansey R; Goessl C

INSTITUCIÓN / INSTITUTION: - Matthew R. Smith, Massachusetts General Hospital Cancer Center, Boston, MA; Fred Saad, University of Montreal Hospital Center, Montreal, Quebec, Canada; Stephane Oudard, Georges Pompidou Hospital, Paris; Karim Fizazi, Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Neal Shore, Carolina Urological Research Center, Myrtle Beach, SC; Paul Sieber, Urological Associates of Lancaster, Lancaster, PA; Bertrand Tombal, Universite Catholique de Louvain Cliniques Universitaires Saint Luc, Bruxelles, Belgium; Ronaldo Damiao, Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil; Gavin Marx, Sydney Haematology and Oncology Clinic, University of Sydney, Wahroonga, New South Wales, Australia; Kurt Miller, Charite Berlin, Berlin, Germany; Peter Van Veldhuizen, Kansas City Veterans Affairs Medical Center, Kansas City, MO; Juan Morote, Hospital Vall d'Hebron, Barcelona, España; and Zhishen Ye, Roger Dansey, and Carsten Goessl, Amgen, Thousand Oaks, CA.

RESUMEN / SUMMARY: - PURPOSE: Denosumab, an anti-RANK ligand monoclonal antibody, significantly increases bone metastasis-free survival (BMFS; hazard ratio [HR], 0.85; P = .028) and delays time to first bone metastasis in men with nonmetastatic castration-resistant prostate cancer (CRPC) and baseline prostate-specific antigen (PSA) \geq 8.0 ng/mL and/or PSA doubling time (PSADT) \leq 10.0 months. To identify men at greatest risk for bone metastasis or death, we evaluated relationships between PSA and PSADT with BMFS in the placebo group and the efficacy and safety of denosumab in men with PSADT \leq 10, \leq 6, and \leq 4 months. PATIENTS AND METHODS: A total of 1,432 men with nonmetastatic CRPC were

randomly assigned 1:1 to monthly subcutaneous denosumab 120 mg or placebo. Enrollment began February 2006; primary analysis cutoff was July 2010, when approximately 660 men were anticipated to have developed bone metastases or died. RESULTS: In the placebo group, shorter BMFS was observed as PSADT decreased below 8 months. In analyses by shorter baseline PSADT, denosumab consistently increased BMFS by a median of 6.0, 7.2, and 7.5 months among men with PSADT \leq 10 (HR, 0.84; P = .042), \leq 6 (HR, 0.77; P = .006), and \leq 4 months (HR, 0.71; P = .004), respectively. Denosumab also consistently increased time to bone metastasis by PSADT subset. No difference in survival was observed between treatment groups for the overall study population or PSADT subsets. CONCLUSION: Patients with shorter PSADT are at greater risk for bone metastasis or death. Denosumab consistently improves BMFS in men with shorter PSADT and seems to have the greatest treatment effects in men at high risk for progression.

[118]

TÍTULO / TITLE: - Tamoxifen and Risk of Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 1;31(25):3091-3099. Epub 2013 Aug 5.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2012.47.8313](#)

AUTORES / AUTHORS: - Phillips KA; Milne RL; Rookus MA; Daly MB; Antoniou AC; Peock S; Frost D; Easton DF; Ellis S; Friedlander ML; Buys SS; Andrieu N; Nogues C; Stoppa-Lyonnet D; Bonadona V; Pujol P; McLachlan SA; John EM; Hooning MJ; Seynaeve C; Tollenaar RA; Goldgar DE; Terry MB; Caldes T; Weideman PC; Andrulis IL; Singer CF; Birch K; Simard J; Southey MC; Olsson HL; Jakubowska A; Olah E; Gerdes AM; Foretova L; Hopper JL

INSTITUCIÓN / INSTITUTION: - Kelly-Anne Phillips, Sue Anne McLachlan, Prue C. Weideman, and Kate Birch, Peter MacCallum Cancer Centre; Kelly-Anne Phillips, Roger L. Milne, Sue Anne McLachlan, Melissa C. Southey, and John L. Hopper, University of Melbourne; Sue Anne McLachlan, St Vincent's Hospital, Melbourne, Victoria; Michael L. Friedlander, Prince of Wales Hospital, Randwick, New South Wales, Australia; Roger L. Milne, Spanish National Cancer Research Centre; Trinidad Caldes, Hospital Clinico San Carlos, Instituto de Investigacion Sanitaria San Carlos, Madrid, España; Matti A. Rookus, Netherlands Cancer Institute, Amsterdam; Maartje Hooning and Caroline Seynaeve, Erasmus University Medical Center-Daniel den Hoed Cancer Center, Rotterdam; Rob A.E.M. Tollenaar, Leiden University Medical Centre, Leiden, the Netherlands; Mary B. Daly, Fox Chase Cancer Center, Philadelphia, PA; Antonis C. Antoniou, Susan Peock, Debra Frost, Douglas F. Easton, Steve Ellis, University of Cambridge, Cambridge, United Kingdom; Sandra S. Buys and David Goldgar, Huntsman Cancer Institute at the University of Utah, UT; Nadine Andrieu and

Dominique Stoppa-Lyonnet, Institut Curie; Nadine Andrieu, L'Institut National de la Sante et de la Recherche Medicale, U900; Dominique Stoppa-Lyonnet, L'Institut National de la Sante et de la Recherche Medicale, U830; Dominique Stoppa-Lyonnet, Universite Paris-Descartes, Paris; Nadine Andrieu, Mines ParisTech, Fontainebleau; Catherine Nogues, Institut Curie, Hopital Rene Huguenin, St Cloud; Valerie Bonadona, Universite Lyon 1; Valerie Bonadona, Centre National de la Recherche Scientifique Unite Mixte de Recherche 5558; Valerie Bonadona, Centre Leon Berard, Lyon; Pascal Pujol, Centre Hospitalier Universitaire Arnaud de Villeneuve; Pascal Pujol, L'Institut National de la Sante et de la Recherche Medicale 896, Centre de Recherche en Cancerologie de Marseille Val d'Aurelle, Montpellier, France; Esther M. John, Cancer Prevention Institute of California, Fremont; Esther M. John, Stanford University School of Medicine, Stanford, CA; Mary Beth Terry, Columbia University, New York, NY; Irene L. Andrulis, University of Toronto, Toronto, Ontario; Jacques Simard, Centre Hospitalier Universitaire de Quebec and Laval University, Quebec City, Quebec, Canada; Christian F. Singer, Medical University of Vienna, Vienna, Austria; Hakan Olsson, Lund University, Lund, Sweden; Anna Jakubowska, Pomeranian Medical University, Szczecin, Poland; Edith Olah, National Institute of Oncology, Budapest, Hungary; Anne-Marie Gerdes, Rigshospitalet and Copenhagen University, Copenhagen, Denmark; and Lenka Foretova, Masaryk Memorial Cancer Institute, Brno, Czech Republic.

RESUMEN / SUMMARY: - PURPOSE: To determine whether adjuvant tamoxifen treatment for breast cancer (BC) is associated with reduced contralateral breast cancer (CBC) risk for BRCA1 and/or BRCA2 mutation carriers. METHODS: Analysis of pooled observational cohort data, self-reported at enrollment and at follow-up from the International BRCA1, and BRCA2 Carrier Cohort Study, Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer, and Breast Cancer Family Registry. Eligible women were BRCA1 and BRCA2 mutation carriers diagnosed with unilateral BC since 1970 and no other invasive cancer or tamoxifen use before first BC. Hazard ratios (HRs) for CBC associated with tamoxifen use were estimated using Cox regression, adjusting for year and age of diagnosis, country, and bilateral oophorectomy and censoring at contralateral mastectomy, death, or loss to follow-up. RESULTS: Of 1,583 BRCA1 and 881 BRCA2 mutation carriers, 383 (24%) and 454 (52%), respectively, took tamoxifen after first BC diagnosis. There were 520 CBCs over 20,104 person-years of observation. The adjusted HR estimates were 0.38 (95% CI, 0.27 to 0.55) and 0.33 (95% CI, 0.22 to 0.50) for BRCA1 and BRCA2 mutation carriers, respectively. After left truncating at recruitment to the cohort, adjusted HR estimates were 0.58 (95% CI, 0.29 to 1.13) and 0.48 (95% CI, 0.22 to 1.05) based on 657 BRCA1 and 426 BRCA2 mutation carriers with 100 CBCs over 4,392 person-years of prospective follow-up. HRs did not differ by estrogen receptor status of the first BC (missing for 56% of cases). CONCLUSION: This study provides evidence that tamoxifen use is associated with a reduction in CBC risk for BRCA1 and BRCA2 mutation carriers.

Further follow-up of these cohorts will provide increased statistical power for future prospective analyses.

[119]

TÍTULO / TITLE: - Clonal Heterogeneity As Detected by Metaphase Karyotyping Is an Indicator of Poor Prognosis in Acute Myeloid Leukemia.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 23.

●● [Enlace al texto completo \(gratis o de pago\) 1200/JCO.2013.50.7921](#)

AUTORES / AUTHORS: - Bochtler T; Stolzel F; Heilig CE; Kunz C; Mohr B; Jauch A; Janssen JW; Kramer M; Benner A; Bornhauser M; Ho AD; Ehninger G; Schaich M; Kramer A

INSTITUCIÓN / INSTITUTION: - Tilmann Bochtler, Christoph E. Heilig, Anna Jauch, Johannes W.G. Janssen, Anthony D. Ho, and Alwin Kramer, University of Heidelberg; Tilmann Bochtler, Christina Kunz, Axel Benner, and Alwin Kramer, German Cancer Research Center (DKFZ), Heidelberg; and Friedrich Stolzel, Brigitte Mohr, Michael Kramer, Martin Bornhauser, Gerhard Ehninger, and Markus Schaich, University Hospital Carl Gustav Carus, Dresden, Germany.

RESUMEN / SUMMARY: - **PURPOSE:** In acute myeloid leukemia (AML), studies based on whole-genome sequencing have shown genomic diversity within leukemic clones. The aim of this study was to address clonal heterogeneity in AML based on metaphase cytogenetics. **PATIENTS AND METHODS:** This analysis included all patients enrolled onto two consecutive, prospective, randomized multicenter trials of the Study Alliance Leukemia. Patients were newly diagnosed with non-M3 AML and were fit for intensive chemotherapy. **RESULTS:** Cytogenetic subclones were detected in 418 (15.8%) of 2,639 patients from the whole study population and in 418 (32.8%) of 1,274 patients with aberrant karyotypes. Among those, 252 karyotypes (60.3%) displayed a defined number of distinct subclones, and 166 (39.7%) were classified as composite karyotypes. Subclone formation was particularly frequent in the cytogenetically adverse group, with subclone formation in 69.0%, 67.1%, and 64.8% of patients with complex aberrant, monosomal, and abn(17p) karyotypes ($P < .001$ each). Two-subclone patterns typically followed a mother-daughter evolution, whereas for \geq three subclones, a branched pattern prevailed. In non-core binding factor AML, subclone formation was associated with inferior event-free and overall survival and was confirmed as an independent predictor of poor prognosis in multivariate analysis. Subgroup analysis showed that subclone formation adds prognostic information particularly in the cytogenetic adverse-risk group. Allogeneic stem-cell transplantation improved the prognosis of patients with subclone karyotypes as shown in landmark analyses. **CONCLUSION:** Cytogenetic subclones are frequent in AML and permit tracing of clonal evolution and architecture. They bear prognostic significance with clonal

heterogeneity as an independent adverse prognostic marker in cytogenetically adverse-risk AML.

[120]

TÍTULO / TITLE: - Analysis of cytotoxic T lymphocytes from a patient with hepatocellular carcinoma who showed a clinical response to vaccination with a glypican3derived peptide.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1019-26. doi: 10.3892/ijo.2013.2044. Epub 2013 Jul 31.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2044](#)

AUTORES / AUTHORS: - Tada Y; Yoshikawa T; Shimomura M; Sawada Y; Sakai M; Shirakawa H; Nobuoka D; Nakatsura T

INSTITUCIÓN / INSTITUTION: - Division of Cancer Immunotherapy, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba 2778577, Japan.

RESUMEN / SUMMARY: - Glypican-3 (GPC3), which is a carcinoembryonic antigen, is overexpressed in human hepatocellular carcinoma (HCC). Previously, we performed a phase I clinical trial of GPC3derived peptide vaccination in patients with advanced HCC, and reported that GPC3 peptide vaccination is safe and has clinical efficacy. Moreover, we proposed that a peptidespecific CTL response is a predictive marker of overall survival in patients with HCC who receive peptide vaccination. In this study, we established GPC3derived peptidespecific CTL clones from the PBMCs of an HLA*02:07positive patient with HCC who was vaccinated with an HLA*02:07restricted GPC3 peptide vaccine and showed a clinical response in the phase I clinical trial. Established CTL clones were analyzed using the IFNgamma ELISPOT assay and a cytotoxicity assay. GPC3 peptidespecific CTL clones were established successfully from the PBMCs of the patient. One CTL clone showed cytotoxicity against cancer cell lines that expressed endogenously the GPC3 peptide. The results suggest that CTLs have high avidity, and that natural antigenspecific killing activity against tumor cells can be induced in a patient with HCC who shows a clinical response to vaccination with the GPC3144152 peptide.

[121]

TÍTULO / TITLE: - Transformation to small-cell lung cancer following treatment with EGFR tyrosine kinase inhibitors in a patient with lung adenocarcinoma.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Sep 5. pii: S0169-5002(13)00260-2. doi: 10.1016/j.lungcan.2013.06.003.

●● Enlace al texto completo (gratuito o de pago) [1016/j.lungcan.2013.06.003](https://doi.org/10.1016/j.lungcan.2013.06.003)

AUTORES / AUTHORS: - Watanabe S; Sone T; Matsui T; Yamamura K; Tani M; Okazaki A; Kurokawa K; Tambo Y; Takato H; Ohkura N; Waseda Y; Katayama N; Kasahara K

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, Ishikawa, Japan.

RESUMEN / SUMMARY: - We report the case of a 52-year-old woman with lung adenocarcinoma treated with EGFR tyrosine kinase inhibitor (TKI) therapy. After disease progression, histological examination of a secondary biopsy specimen revealed small-cell lung cancer (SCLC) that was sensitive to standard SCLC treatment. Tumor markers, including ProGRP and NSE, were elevated. Transformation to SCLC is a mechanism for acquired resistance to EGFR-TKI therapy. Secondary biopsy is important for evaluation of genetic and histological changes and selection of appropriate treatment. Furthermore, ProGRP and NSE may be useful for early detection of SCLC transformation in cases resistant to EGFR-TKI therapy.

[122]

TÍTULO / TITLE: - Prediction value of intercellular adhesion molecule-1 gene polymorphisms for epithelial ovarian cancer risk, clinical features, and prognosis.

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

REVISTA / JOURNAL: - Gene. 2013 Aug 7. pii: S0378-1119(13)00957-8. doi: 10.1016/j.gene.2013.07.049.

●● Enlace al texto completo (gratuito o de pago) [1016/j.gene.2013.07.049](https://doi.org/10.1016/j.gene.2013.07.049)

AUTORES / AUTHORS: - Cai G; Ma X; Zou W; Huang Y; Zhang J; Wang D; Chen B

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Xijing Hospital, Fourth Military Medical University, No. 17 Changle West Road, Xi'an 710032, PR China.

RESUMEN / SUMMARY: - Intercellular adhesion molecule-1 (ICAM-1, encoded by ICAM-1) is implicated in tumorigenesis and tumor progression. ICAM-1 modulates the susceptibility to several types of cancer and the disease prognosis; however, its role in epithelial ovarian cancer (EOC) is unclear. Here, we evaluate single nucleotide polymorphisms (SNPs) in ICAM-1 as predictors of EOC risk and prognosis. Six ICAM-1 polymorphisms were genotyped in 408 patients with EOC and 520 controls using the MassARRAY system. The ICAM-1 mRNA levels in 89 EOC tissues and 35 normal ovarian tissues were examined using quantitative PCR. The ICAM-1 rs5498 G allele was associated with increased tumor grade (OR=2.650) and EOC risk (OR=1.405). This risk was more evident in females who had first-degree relatives (FDRs) with a tumor (OR=3.475) or who experienced early menarche (OR=2.774). The ICAM-1 expression in the cancerous tissue was elevated compared with that of normal ovarian tissues ($p < 0.0001$), and it was associated with an rs5498 genotype ($p = 0.0002$). ICAM-1 SNPs did not significantly predict the overall EOC survival ($p > 0.05$). However, the rs5498 G

allele correlated with EOC survival time in patients whose FDRs suffered from a tumor (p=0.001). ICAM-1 rs5498 likely confers a high risk for EOC in G allele carriers accompanied by up-regulation of ICAM-1 expression during carcinogenesis. The combination of ICAM-1 rs5498 and tumor history predicts the EOC prognosis.

[123]

TÍTULO / TITLE: - Comet assay measures of DNA damage are predictive of bladder cancer cell treatment sensitivity in vitro and outcome in vivo.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 19. doi: 10.1002/ijc.28437.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28437](#)

AUTORES / AUTHORS: - Bowman KJ; Al-Moneef MM; Sherwood BT; Colquhoun AJ; Goddard JC; Griffiths TR; Payne D; Singh S; Butterworth PC; Khan MA; Summerton DJ; Steward WP; McKelvey-Martin VJ; McKeown SR; Kockelbergh RC; Mellon JK; Symonds RP; Jones GD

INSTITUCIÓN / INSTITUTION: - Department of Cancer Studies & Molecular Medicine, University of Leicester, Leicester, UK.

RESUMEN / SUMMARY: - Bladder cancer patients suffer significant treatment failure, including high rates of recurrence and poor outcomes for advanced disease. If mechanisms to improve tumour cell treatment sensitivity could be identified and/or if tumour response could be predicted, it should be possible to improve local-control and survival. Previously, we have shown that radiation-induced DNA damage, measured by alkaline Comet assay (ACA), correlates bladder cancer cell radiosensitivity in vitro. In the present study we firstly show that modified-ACA measures of cisplatin and mitomycin-C-induced damage also correlate bladder cancer cell chemosensitivity in vitro, with essentially the same rank order for chemosensitivity as for radiosensitivity. Furthermore, ACA studies of radiation-induced damage in different cell-DNA substrates (nuclei, nucleoids & intact parent cells) suggest that it is a feature retained in the prepared nucleoids that is responsible for the relative damage sensitivity of bladder cancer cells, suggestive of differences in the organisation of DNA within resistant vs. sensitive cells. Secondly, we show that ACA analysis of biopsies from bladder tumours reveal that reduced DNA damage sensitivity associates with poorer treatment outcomes, notably that tumours with a reduced damage response show a significant association with local recurrence of non-invasive disease and that reduced damage response was a better predictor of recurrence than the presence of high-risk histology in this cohort. In conclusion, this study demonstrates that mechanisms governing treatment-induced DNA damage are both central to and predictive of bladder cancer cell treatment sensitivity and exemplifies a link between DNA damage resistance and both treatment response and tumour aggression. © 2013 Wiley Periodicals, Inc.

[124]

TÍTULO / TITLE: - Phosphodiesterase 5 inhibitor acts as a potent agent sensitizing acute myeloid leukemia cells to 67-kDa laminin receptor-dependent apoptosis.

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

REVISTA / JOURNAL: - FEBS Lett. 2013 Sep 17;587(18):3052-7. doi: 10.1016/j.febslet.2013.07.041. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1016/j.febslet.2013.07.041](#)

AUTORES / AUTHORS: - Kumazoe M; Kim Y; Bae J; Takai M; Murata M; Suemasu Y; Sugihara K; Yamashita S; Tsukamoto S; Huang Y; Nakahara K; Yamada K; Tachibana H

INSTITUCIÓN / INSTITUTION: - Division of Applied Biological Chemistry, Department of Bioscience and Biotechnology, Faculty of Agriculture, Kyushu University, Fukuoka 812-8581, Japan.

RESUMEN / SUMMARY: - (-)-Epigallocatechin-3-O-gallate (EGCG), a polyphenol in green tea, induces apoptosis in acute myeloid leukemia (AML) cells without affecting normal cells. In this study, we observed that cGMP acts as a cell death mediator of the EGCG-induced anti-AML effect through acid sphingomyelinase activation. EGCG activated the Akt/eNOS axis, a well-known mechanism in vascular cGMP upregulation. We also observed that a major cGMP negative regulator, phosphodiesterase 5, was overexpressed in AML cells, and PDE5 inhibitor, an anti-erectile dysfunction drug, synergistically enhanced the anti-AML effect of EGCG. This combination regimen killed AML cells via overexpressed 67-kDa laminin receptors.

[125]

TÍTULO / TITLE: - Emergence of polyclonal FLT3 tyrosine kinase domain mutations during sequential therapy with sorafenib and sunitinib in FLT3-ITD-positive acute myeloid leukemia.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1323](#)

AUTORES / AUTHORS: - Baker SD; Zimmerman EI; Wang YD; Orwick S; Zatechka DS; Buaboonnam J; Neale G; Olsen SR; Enemark EJ; Shurtleff S; Rubnitz J; Mullighan CG; Inaba H

INSTITUCIÓN / INSTITUTION: - Pharmaceutical Sciences, St. Jude Children's Research Hospital.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the clinical activity of sequential therapy with sorafenib and sunitinib in FLT3-ITD-positive AML and monitor the emergence of secondary FLT3 tyrosine kinase domain (TKD) mutations during treatment.

EXPERIMENTAL DESIGN: Six children with relapsed/refractory AML were treated with

sorafenib in combination with clofarabine and cytarabine, followed by single-agent sorafenib if not a candidate for transplantation. Sunitinib was initiated after sorafenib relapse. Bone marrow samples were obtained for assessment of FLT3 TKD mutations by deep amplicon sequencing. The phase of secondary mutations with ITD alleles was assessed by cloning and sequencing of FLT3 exons 14 through 20. Identified mutations were modeled in Ba/F3 cells and the effect of kinase inhibitors on FLT3 signaling and cell viability was assessed. RESULTS: Four patients achieved complete remission, but 3 receiving maintenance therapy with sorafenib relapsed after 14-37 weeks. Sunitinib reduced circulating blasts in 2 patients and marrow blasts in 1. Two patients did not respond to sorafenib combination therapy or sunitinib. FLT3 mutations at residues D835 and F691 were observed in sorafenib resistance samples on both ITD-positive and -negative alleles. Deep sequencing revealed low-level mutations and their evolution during sorafenib treatment. Sunitinib suppressed leukemic clones with D835H and F691L mutations, but not D835Y. Cells expressing sorafenib-resistant FLT3 mutations were sensitive to sunitinib in vitro. CONCLUSIONS: Sunitinib has activity in patients that are resistant to sorafenib and harbor secondary FLT3 TKD mutations. The use of sensitive methods to monitor FLT3 mutations during therapy may allow individualized treatment with the currently available kinase inhibitors. -

[126]

TÍTULO / TITLE: - Role of mitogen-activated protein kinases and Mcl-1 in apoptosis induction by withaferin A in human breast cancer cells.

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

REVISTA / JOURNAL: - Mol Carcinog. 2013 Sep 9. doi: 10.1002/mc.22050.

●● [Enlace al texto completo \(gratis o de pago\) 1002/mc.22050](#)

AUTORES / AUTHORS: - Hahn ER; Lee J; Singh SV

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Chemical Biology, and University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

RESUMEN / SUMMARY: - Withaferin A (WA), a bioactive constituent of Ayurvedic medicine plant *Withania somnifera*, is a potent apoptosis inducer in cancer cells but the mechanism of cell death induction is not fully characterized. The present study was undertaken to determine the role of mitogen-activated protein kinases (MAPK), including c-jun NH2-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 MAPK, and anti-apoptotic protein myeloid cell leukemia-1 (Mcl-1) in regulation of WA-induced apoptosis using human breast cancer cells. Exposure of MCF-7 (estrogen responsive) and SUM159 (triple negative) human breast cancer cells to WA resulted in increased phosphorylation of ERK, JNK, and p38 MAPK, but these effects were relatively more pronounced in the former cell line than in SUM159. Overexpression of manganese-superoxide dismutase conferred partial protection

against WA-mediated hyperphosphorylation of ERK, but not JNK or p38 MAPK. Cell death resulting from WA treatment in MCF-7 cells was significantly augmented by pharmacological inhibition of ERK and p38 MAPK. Interestingly, the WA-induced apoptosis in MCF-7 cells was partially but significantly blocked in the presence of a JNK-specific inhibitor. Pharmacological inhibition of ERK or JNK had no effect on WA-induced apoptosis in SUM159 cells. The WA-treated cells exhibited induction of long and short forms of Mcl-1. RNA interference of Mcl-1 alone triggered apoptosis. Furthermore, the WA-induced cell death in MCF-7 cells was modestly but significantly augmented by knockdown of the Mcl-1 protein. These observations indicate that: MAPK have cell line-specific role in cell death by WA, and Mcl-1 induction confers modest protection against WA-induced apoptosis. © 2013 Wiley Periodicals, Inc.

[127]

TÍTULO / TITLE: - Phase 1 pharmacokinetic study of MK-0646 (dalotuzumab), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in combination with cetuximab and irinotecan in Japanese patients with advanced colorectal cancer.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep;72(3):643-52. doi: 10.1007/s00280-013-2240-8. Epub 2013 Aug 7.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2240-8](#)

AUTORES / AUTHORS: - Doi T; Muro K; Yoshino T; Fuse N; Ura T; Feng HP; Shimamoto T; Noguchi K; Ohtsu A

INSTITUCIÓN / INSTITUTION: - National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan, tdoi@east.ncc.go.jp.

RESUMEN / SUMMARY: - PURPOSE: The safety, tolerability, and pharmacokinetic (PK) interactions of MK-0646 in combination with cetuximab and irinotecan were investigated in Japanese patients with advanced colorectal cancer. METHODS: Twenty patients were treated in the following study arms in combination with cetuximab and irinotecan: A [MK-0646 (10 mg/kg) weekly starting on Day 22], B [MK-0646 (15 mg/kg) on Day 8, followed by 7.5 mg/kg every 2 weeks], or C [MK-0646 (10 mg/kg) on Day 1 and weekly starting on Day 22]. Dose limiting toxicities (DLTs) were evaluated during a prespecified 4-week period in arms A and B. Full PK sampling was performed to evaluate the PK interactions. RESULTS: One of the 6 evaluable patients in arm A developed a DLT (grade 3 hyperglycemia); no DLTs occurred in the 6 patients in arm B. Common treatment-related adverse events included leukopenia, neutropenia, dermatitis acneiform, paronychia, nausea, stomatitis, diarrhea, and decreased appetite. The co-administration of cetuximab and irinotecan with MK-0646 increased the MK-0646 AUC_{0-168h} by 25 %, with MK-0646 accumulation from the previous dose contributing to the observed increase. The co-administration of MK-0646 with cetuximab and irinotecan did not affect the PK of cetuximab and irinotecan, but

reduced the C max (from 16.8 to 13.0 ng/mL) and the AUC0-24h (by 13 %) of SN-38, the active metabolite of irinotecan. CONCLUSIONS: The triple combination of MK-0646, cetuximab, and irinotecan was well tolerated in Japanese patients with advanced colorectal cancer. These results indicate a minimal potential for PK interactions between MK-0646 and cetuximab and between MK-0646 and irinotecan/SN-38.

PTPTPTP - Journal Article

[128]

TÍTULO / TITLE: - Results of treatment with azacitidine in patients aged \geq 75 years included in the Spanish Registry of Myelodysplastic Syndromes.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 16.

●● [Enlace al texto completo \(gratis o de pago\) 3109/10428194.2013.834532](#)

AUTORES / AUTHORS: - Xicoy B; Jimenez MJ; Garcia O; Bargay J; Martinez-Robles V; Brunet S; Arilla MJ; Perez de Oteyza J; Andreu R; Casano FJ; Cervero CJ; Bailen A; Diez M; Gonzalez B; Vicente AI; Pedro C; Bernal T; Luno E; Cedena MT; Palomera L; Simiele A; Calvo JM; Marco V; Gomez E; Gomez M; Gallardo D; Munoz J; de Paz R; Grau J; Ribera JM; Benlloch LE; Sanz G

INSTITUCIÓN / INSTITUTION: - Hematology Department of Institut Catala d'Oncologia, Josep Carreras Research Institute - Hospital Germans Trias i Pujol, Badalona, España.

RESUMEN / SUMMARY: - The tolerability of azacitidine (AZA) allows its administration in elderly patients. The objective of this study was to analyze the clinical and biological characteristics, transfusion independence (TI), overall survival (OS) and toxicity in a series of 107 patients \geq 75 years of age from the Spanish Registry of Myelodysplastic Syndromes (MDS) treated with AZA. The median age (range) was 78 (75-90) years. According to the World Health Organization (WHO) classification, 86/102 (84%) had MDS, 10/102 (10%) had mixed myeloproferative/myelodysplastic disorder and 6/102 (6%) had acute myeloblastic leukemia. Regarding MDS by the International Prognostic Scoring System on initiation of AZA, 38/84 (45%) were low-intermediate-1 risk and 46/84 (55%) were intermediate-2-high risk. Ninety-five patients (89%) were red blood cell or platelet transfusion dependent. The AZA schedule was 5-0-0 in 39/106 (37%) patients, 5-2-2 in 36/106 (34%) patients and 7 consecutive days in 31/106 (29%) patients. The median number of cycles administered was 8 (range, 1-30). Thirty-eight out of 94 (40%) patients achieved TI. Median OS (95% confidence interval [CI]) was significantly better in patients achieving TI (n = 38) compared to patients who did not (n = 56) (22 [20.1-23.9] months vs. 11.1 [4.8-17.5] months, p = 0.001). No significant differences were observed in TI rate and OS among the three different schedules. With a median follow-up of 14 (min-max, 1-50) months, the median OS (95% CI) of the 107 patients was 18 (12-23) months and the probability of OS (95% CI) at 2 years was 34%

(22-46%). Cycles were delayed in 31/106 (29%) patients and 47/101 patients (47%) were hospitalized for infection. These results show that treatment with AZA was feasible and effective in this elderly population, with 40% achieving TI, having a better OS than patients not achieving it. The schedule of AZA administration did not affect efficacy and toxicity.

[129]

TÍTULO / TITLE: - Pro-angiogenic cytokines for prediction of outcomes in patients with advanced hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17. doi: 10.1038/bjc.2013.554.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.554](#)

AUTORES / AUTHORS: - Miyahara K; Nouse K; Morimoto Y; Takeuchi Y; Hagihara H; Kuwaki K; Onishi H; Ikeda F; Miyake Y; Nakamura S; Shiraha H; Takaki A; Honda M; Kaneko S; Sato T; Sato S; Obi S; Iwadou S; Kobayashi Y; Takaguchi K; Kariyama K; Takuma Y; Takabatake H; Yamamoto K; Yamamoto K; Morimoro Y; Takeuchi Y; Miyahara K; Hagihara H; Kuwaki K; Onishi H; Nakamura S; Shiraha H; Nouse K; Takuma Y; Takabatake H; Morimoto Y; Fujioka S; Osawa T; Kariyama K; Toshimori J; Kobashi H; Miyatake H; Iwadou S; Kobayashi Y; Uematsu S; Okamoto R; Araki Y; Tatsukawa M; Yabushita K; Shimoe T; Sakaguchi K; Sakata T; Kaneyoshi T; Miyashita M; Makino Y; Moriya A; Ando M; Baba N; Seno T; Nagano T; Takaguchi K; Matsumoto E; Takayama H
INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama 700-8558, Japan.

RESUMEN / SUMMARY: - Background: We previously reported that expressions of the pro-angiogenic cytokines angiopoietin-2 (Ang-2), follistatin, granulocyte colony-stimulating factor, hepatocyte growth factor, leptin, platelet-derived growth factor-BB, platelet endothelial cell adhesion molecule-1, and vascular endothelial growth factor were associated with the response to sorafenib in patients with advanced hepatocellular carcinoma (HCC). The aim of the present study is to examine the same relationship in a larger cohort. Methods: In the current retrospective cohort study, we measured serum levels of the eight cytokines in 120 consecutive HCC patients who were treated with sorafenib. We evaluated the effects of increased expression of serum cytokines on progression-free survival (PFS) and overall survival (OS). Results: Elevated expression of Ang-2 correlated both with significantly shorter PFS (hazard ratio (HR), 1.84; 95% confidence interval (CI), 1.21-2.81), and OS (HR, 1.95; 95% CI, 1.21-3.17). Patients with more than three cytokines expressed above the median similarly had significantly shorter PFS (HR, 1.98; 95% CI, 1.30-3.06) and OS (HR, 1.94; 95% CI, 1.19-3.22). Differences in OS were evident in cases with the evidence of macroscopic vascular invasion or extrahepatic metastasis. Conclusion: High expression of Ang-2 or more than

cytokines in serum is associated with poor PFS and OS in HCC patients treated with sorafenib. British Journal of Cancer advance online publication, 17 September 2013; doi:10.1038/bjc.2013.554 www.bjcancer.com.

[130]

TÍTULO / TITLE: - Circulating plasma DNA and DNA integrity in breast cancer patients undergoing neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Clin Chim Acta. 2013 Aug 2;425C:206-211. doi: 10.1016/j.cca.2013.07.027.

●● Enlace al texto completo (gratis o de pago) 1016/j.cca.2013.07.027

AUTORES / AUTHORS: - Lehner J; Stotzer OJ; Fersching D; Nagel D; Holdenrieder S

INSTITUCIÓN / INSTITUTION: - Institute of Clinical Chemistry, University Hospital Munich-Grosshadern, Munich, Germany.

RESUMEN / SUMMARY: - BACKGROUND: In breast cancer patients undergoing neoadjuvant chemotherapy before surgery, biomarkers for predicting response to therapy are urgently required. PATIENTS AND METHODS: In 65 patients with locally confined breast cancer who had completed the course of chemotherapy until surgery, plasma DNA biomarkers obtained before and during therapy were evaluated concerning (early) estimation of therapy response. Levels of repetitive ALU 115 and ALU 247 elements as well as DNA integrity calculated according the formulas of Umetani (1) and Wang (2) were correlated with changes in histopathological staging at surgery and compared with conventional tumor markers CEA and CA 15-3. RESULTS: At surgery, 13 patients presented complete remission (CR), 32 partial remission (PR) and 20 no change of disease (NC). Pretherapeutic Her2/neu status was positively correlated with therapy response ($p=0.019$). DNA biomarkers before onset of therapy cycles 1, 2 and 6 did not indicate outcome after therapy. However, kinetics of ALU 115 from cycle 1 to 6 showed decreases in CR patients, while in NC patients, an increase was observed ($p=0.033$). Similar tendencies were found for ALU 247 fragments. DNA integrity index as well as CEA and CA 15-3 were not informative for therapy outcome. CONCLUSION: Kinetics of plasma DNA (ALU 115) is associated with response to neoadjuvant chemotherapy in patients with locally confined breast cancer.

[131]

TÍTULO / TITLE: - The Herbal Compound Cryptotanshinone Restores Sensitivity in Cancer Cells that are Resistant to the Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.483909](https://doi.org/10.1074/jbc.M113.483909)

AUTORES / AUTHORS: - Tse AK; Chow KY; Cao HH; Cheng CY; Kwan HY; Yu H; Zhu GY; Wu YC; Fong WF; Yu ZL

INSTITUCIÓN / INSTITUTION: - Hong Kong Baptist University, Hong Kong.

RESUMEN / SUMMARY: - Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis and kills cancer cells but not normal cells. However, TRAIL resistance due to low level of TRAIL receptor expression is widely found in cancer cells and hampers its development for cancer treatment. Thus, the agents that can sensitize the tumor cells to TRAIL-mediated apoptosis are urgently needed. We investigated whether tanshinones, the major bioactive compounds of *Salvia miltiorrhiza* (Danshen), can up-regulate TRAIL receptor expression. Among the major tanshinones being tested, cryptotanshinone (CT) showed the best ability to induce TRAIL receptor 2 (DR5) expression. We further showed that CT was capable of promoting TRAIL-induced cell death and apoptosis in A375 melanoma cells. CT-induced DR5 induction was not cell type-specific, as DR5 induction was observed in other cancer cell types. DR5 knockdown abolished the enhancing effect of CT on TRAIL responses. Mechanistically, induction of the DR5 by CT was found to be p53-independent but dependent on the induction of CCAAT/enhancer-binding protein-homologous protein (CHOP). Knockdown of CHOP abolished CT-induced DR5 expression and the associated potentiation of TRAIL-mediated cell death. In addition, CT-induced ROS production preceded up-regulation of CHOP and DR5, and consequent sensitization of cells to TRAIL. Interestingly, CT also converted TRAIL-resistant lung A549 cancer cells into TRAIL-sensitive cells. Taken together, our results indicate that CT can potentiate TRAIL-induced apoptosis through up-regulation of DR5.

[132]

TÍTULO / TITLE: - Phase II Study of Alisertib, a Selective Aurora A Kinase Inhibitor, in Relapsed and Refractory Aggressive B- and T-Cell Non-Hodgkin Lymphomas.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [1200/JCO.2012.46.8793](https://doi.org/10.1200/JCO.2012.46.8793)

AUTORES / AUTHORS: - Friedberg JW; Mahadevan D; Cebula E; Persky D; Lossos I; Agarwal AB; Jung J; Burack R; Zhou X; Leonard EJ; Fingert H; Danaee H; Bernstein SH

INSTITUCIÓN / INSTITUTION: - Jonathan W. Friedberg, Erin Cebula, Richard Burack, and Steven H. Bernstein, University of Rochester Wilmot Cancer Center, Rochester, NY; Daruka Mahadevan, West Clinic and University of Tennessee Health Sciences Center, Memphis, TN; Daniel Persky, Yale University, New Haven, CT; Izidore Lossos, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Amit G. Agarwal, University of Arizona Cancer Center, Tucson, AZ; and JungAh Jung, Xiaofei Zhou, E. Jane

Leonard, Howard Fingert, and Hadi Danaee, Millennium Pharmaceuticals, Cambridge, MA.

RESUMEN / SUMMARY: - PURPOSE: Aurora A kinase (AAK) is overexpressed in aggressive lymphomas and can correlate with more histologically aggressive forms of disease. We therefore designed a phase II study of alisertib, a selective AAK inhibitor, in patients with relapsed and refractory aggressive non-Hodgkin lymphomas. PATIENTS AND METHODS: Patients age \geq 18 years were eligible if they had relapsed or refractory diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma (MCL), transformed follicular lymphoma, Burkitt's lymphoma, or noncutaneous T-cell lymphoma. Alisertib was administered orally at 50 mg twice daily for 7 days in 21-day cycles. RESULTS: We enrolled 48 patients. Histologies included DLBCL (n = 21), MCL (n = 13), peripheral T-cell lymphoma (n = 8), transformed follicular lymphoma (n = 5), and Burkitt's (n = 1). Most common grade 3 to 4 adverse events were neutropenia (63%), leukopenia (54%), anemia (35%), thrombocytopenia (33%), stomatitis (15%), febrile neutropenia (13%), and fatigue (6%). Four deaths during the study were attributed to progressive non-Hodgkin lymphoma (n = 2), treatment-related sepsis (n = 1), and unknown cause (n = 1). The overall response rate was 27%, including responses in three of 21 patients with DLBCL, three of 13 with MCL, one of one with Burkitt's lymphoma, two of five with transformed follicular lymphoma, and four of eight with noncutaneous T-cell lymphoma. The alisertib steady-state trough concentration (n = 25) revealed the expected pharmacokinetic variability, with a trend for higher incidence of adverse event-related dose reductions at higher trough concentrations. Analysis for AAK gene amplification and total AAK protein revealed no differences between histologies or correlation with clinical response. CONCLUSION: The novel AAK inhibitor alisertib seems clinically active in both B- and T-cell aggressive lymphomas. On the basis of these results, confirmatory single-agent and combination studies have been initiated.

[133]

TÍTULO / TITLE: - Surgery decreases number of cells secreting cytotoxic mediators and increases secretion of interleukin 10 in patients with lung cancer.

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

REVISTA / JOURNAL: - Eur J Surg Oncol. 2013 Jul 29. pii: S0748-7983(13)00545-3. doi: 10.1016/j.ejso.2013.07.083.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejso.2013.07.083

AUTORES / AUTHORS: - Rybojad P; Jablonka A; Wilczynska B; Tabarkiewicz J

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RESUMEN / SUMMARY: - AIMS: The phenomenon of immunosuppression induced by surgery is widely described as the adverse impact of surgical interventions on

leukocytes' populations and secretion of several cytokines. Best of our knowledge, we present the first report evaluating the effect of surgical treatment on the specific anti-cancer immune response against tumour antigens. METHODS: The study included 30 patients operated on for lung cancer. Specific secretion of IFN-gamma, Granzyme B, perforines, IL-4, IL-5, IL-10, IL-17^a was assessed by ELISPOT (Enzyme-Linked Immunosorbent Spot Assay). RESULTS: Number of cells secreting IFN-gamma, Granzyme B and perforines under the influence of autologous tumour antigens or mitogens was significantly decreased on the first day after surgery. During the postoperative recovery we observed an increase in the number of cells secreting IFN-gamma, but on the 7th day it still remained lower than before the operation. On the 28th postoperative day it reached a level which was not significantly higher than before the surgery. On the 1st and 7th postoperative day we discovered a significant increase in IL-10 secretion, in response to autologous tumour antigens. CONCLUSIONS: Our results suggest an immunosuppressive effect of surgery on the specific and nonspecific immune stimulation. This effect is particularly expressed in relation to Th1-type immunological response which is associated with direct elimination of cancer cells. Another unfavourable observation is elevated secretion of immunosuppressive IL-10 in response to cancer antigens. These phenomena are associated with shorter survival of the patients.

[134]

TÍTULO / TITLE: - Noninvasive phosphorus magnetic resonance spectroscopic imaging predicts outcome to first-line chemotherapy in newly diagnosed patients with diffuse large B-cell lymphoma.

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

REVISTA / JOURNAL: - Acad Radiol. 2013 Sep;20(9):1122-9. doi: 10.1016/j.acra.2013.04.013.

●● Enlace al texto completo (gratis o de pago) [1016/j.acra.2013.04.013](#)

AUTORES / AUTHORS: - Arias-Mendoza F; Payne GS; Zakian K; Stubbs M; O'Connor OA; Mojahed H; Smith MR; Schwarz AJ; Shukla-Dave A; Howe F; Poptani H; Lee SC; Pettengel R; Schuster SJ; Cunningham D; Heerschap A; Glickson JD; Griffiths JR; Koutcher JA; Leach MO; Brown TR

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Columbia University, 710 W 168th St., Neurological Institute Basement, Room B-057, New York, NY 10032, USA.

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RESUMEN / SUMMARY: - RATIONALE AND OBJECTIVES: Based on their association with malignant proliferation, using noninvasive phosphorus MR spectroscopic imaging ((³¹P) MRSI), we measured the tumor content of the phospholipid-related phosphomonoesters (PME), phosphoethanolamine and phosphocholine, and its correlation with treatment outcome in newly diagnosed patients with diffuse large B-

cell lymphoma (DLBCL) receiving standard first-line chemotherapy. EXPERIMENTAL DESIGN: The PME value normalized to nucleoside triphosphates (PME/NTP) was measured using (31)P MRSI in tumor masses of 20 patients with DLBCL before receiving standard first-line chemotherapy. Response at 6 months was complete in 13 patients and partial in seven. Time to treatment failure (TTF) was ≤ 11 months in eight patients, from 18 to 30 months in three, and ≥ 60 months in nine. RESULTS: On a t test, the pretreatment tumor PME/NTP mean value (SD, n) of patients with a complete response at 6 months was 1.42 (0.41, 13), which was significantly different from the value of 2.46 (0.40, 7) in patients with partial response ($P < .00001$). A Fisher test significantly correlated the PME/NTP values with response at 6 months (sensitivity and specificity at 0.85, $P < .004$) while a Cox proportional hazards regression significantly correlated the PME/NTP values with TTF (hazard ratio = 5.21, $P < .02$). A Kaplan-Meier test set apart a group entirely composed of patients with TTF ≤ 11 months (hazard ratio = 8.66, $P < .00001$). CONCLUSIONS: The pretreatment tumor PME/NTP values correlated with response to treatment at 6 months and time to treatment failure in newly diagnosed patients with DLBCL treated with first-line chemotherapy, and therefore they could be used to predict treatment outcome in these patients.

[135]

TÍTULO / TITLE: - Potential of dihydropyrimidine dehydrogenase genotypes in personalizing 5-Fluorouracil therapy among colorectal cancer patients.

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

REVISTA / JOURNAL: - Ther Drug Monit. 2013 Oct;35(5):624-30. doi: 10.1097/FTD.0b013e318290acd2.

●● Enlace al texto completo (gratis o de pago) [1097/FTD.0b013e318290acd2](#)

AUTORES / AUTHORS: - Teh LK; Hamzah S; Hashim H; Bannur Z; Zakaria ZA; Hasbullani Z; Shia JK; Fijeraid H; Md Nor A; Zailani M; Ramasamy P; Ngow H; Sood S; Salleh MZ

INSTITUCIÓN / INSTITUTION: - *Pharmacogenomics Centre, Faculty of Pharmacy, Universiti Teknologi MARA; daggerDepartment of Biomedical Science, Faculty of Medicine and Health Sciences, University Putra Malaysia, Selangor, Malaysia; double daggerDepartment of Surgery, Kulliyah of Medicine, International Islamic University Malaysia, Kuantan, Malaysia; and section signDepartment of Surgery, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia.

RESUMEN / SUMMARY: - BACKGROUND: Dihydropyrimidine dehydrogenase (DPD) is a pyrimidine catabolic enzyme involved in the initial and rate-limiting step of the catabolic pathway of toxic metabolites of 5-fluorouracil (5-FU). Several studies have reported that deficiency of DPD and polymorphisms of its gene are related to 5-FU toxicities and death. Association between serum concentration of 5-FU and its related toxicity has also been previously demonstrated. Hence, this study aims to understand

the role of DPYD variants in serum level of 5-FU and the risk of developing toxicity to prevent adverse reactions and maximize therapy outcome for personalized medicine. METHODS: A total of 26 patients comprising 3 different ethnic groups (Malay, Chinese, and Indian) diagnosed with colorectal cancer and treated with 5-FU chemotherapy regimen from local hospital were recruited. Polymerase chain reaction and denaturing high-performance liquid chromatography methods were developed to screen polymorphisms of DPYD gene. High-performance liquid chromatography-based quantification assay was developed to measure the serum concentration of 5-FU among these patients. RESULTS: Patients with DPYD genotypes of deficient enzyme activity had higher median serum levels of 5-FU compared with normal DPD group (median, 11.51 mcg/mL; 95% confidence interval, 10.18-16.11 versus median, 0.83 mcg/mL; 95% confidence interval, 0.55-5.90, Mann-Whitney U test; P = 0.010). Patients with neutropenia (n = 11) had significantly higher serum concentrations of 5-FU as compared with those with normal white blood cell count (n = 15) (Mann-Whitney U test, P = 0.031). Combined regression analysis showed that the predictive power of DPYD*5 (rs1801159) and 1896 T>C (rs17376848) for serum concentrations of 5-FU in the studied group was 36.6% (P = 0.04). Similarly, DPYD*5 and 1896 T>C accounted for 29.9% of the occurrences of neutropenia (analysis of variance, P = 0.017). CONCLUSIONS: This study revealed that DPYD*5 (rs1801159) and 1896 T>C (rs17376848) are potentially useful predictive markers of patients' responses to 5-FU chemotherapy. Pharmacogenotyping is therefore recommended to guide dosing of 5-FU and prevent neutropenia.

[136]

TÍTULO / TITLE: - Vorinostat in combination with bortezomib in patients with advanced malignancies directly alters transcription of target genes.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep;72(3):661-7. doi: 10.1007/s00280-013-2242-6. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2242-6](#)

AUTORES / AUTHORS: - Kolesar JM; Traynor AM; Holen KD; Hoang T; Seo S; Kim K; Alberti D; Espinoza-Delgado I; Wright JJ; Wilding G; Bailey HH; Schelman WR

INSTITUCIÓN / INSTITUTION: - University of Wisconsin Carbone Comprehensive Cancer Center, 600 Highland Avenue, K4/554 CSC, Madison, WI, 53792, USA, jmkolesar@pharmacy.wisc.edu.

RESUMEN / SUMMARY: - INTRODUCTION: Vorinostat is a small molecule inhibitor of class I and II histone deacetylase enzymes which alters the expression of target genes including the cell cycle gene p21, leading to cell cycle arrest and apoptosis. METHODS: Patients enrolled in a phase I trial were treated with vorinostat alone on day 1 and vorinostat and bortezomib in combination on day 9. Paired biopsies were obtained in

eleven subjects. Blood samples were obtained on days 1 and 9 of cycle 1 prior to dosing and 2 and 6 h post-dosing in all 60 subjects. Gene expression of p21, HSP70, AKT, Nur77, ERB1, and ERB2 was evaluated in peripheral blood mononuclear cells and tissue samples. Chromatin immunoprecipitation of p21, HSP70, and Nur77 was also performed in biopsy samples. RESULTS: In peripheral blood mononuclear cells, Nur77 was significantly and consistently decreased 2 h after vorinostat administration on both days 1 and 9, median ratio of gene expression relative to baseline of 0.69 with interquartile range 0.49-1.04 ($p < 0.001$); 0.28 (0.15-0.7) ($p < 0.001$), respectively, with more pronounced decrease on day 9, when patients received both vorinostat and bortezomib. p21, a downstream target of Nur77, was significantly decreased on day 9, 2 and 6 h after administration of vorinostat and bortezomib, 0.67 (0.41-1.03) ($p < 0.01$); 0.44 (0.25-1.3) ($p < 0.01$), respectively. The ChIP assay demonstrated a protein-DNA interaction, in this case interaction of Nur77, HSP70 and p21 with acetylated histone H3, at baseline and at day 9 after treatment with vorinostat in tissue biopsies in most patients. CONCLUSION: Vorinostat inhibits Nur77 expression, which in turn may decrease p21 and AKT expression in PBMCs. The influence of vorinostat on target gene expression in tumor tissue was variable; however, most patients demonstrated interaction of acetylated H3 with Nur77, HSP70, and p21 which provides evidence of interaction with the transcriptionally active acetylated H3.

[137]

TÍTULO / TITLE: - Increased expression of the 58-kD microspherule protein (MSP58) is correlated with poor prognosis in glioma patients.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):677. doi: 10.1007/s12032-013-0677-6. Epub 2013 Aug 31.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0677-6](#)

AUTORES / AUTHORS: - Lin W; Li XM; Zhang J; Huang Y; Wang J; Zhang J; Jiang XF; Fei Z

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Xijing Hospital, Fourth Military Medical University, Xi'an, 710032, China.

RESUMEN / SUMMARY: - The pathological grading system for human gliomas is usually used to evaluate the prognosis of glioma patients. However, some glioma patients with similar grades have obvious discrepancies in survival. It is therefore necessary to identify some new certain tumor biomarkers that are more suitable for the prognostic assessment of gliomas than the grading system. The 58-kD microspherule protein (MSP58) is an evolutionarily conserved nuclear protein and plays an important role in the regulation of cell proliferation and malignant transformation. However, whether MSP58 can be used as a biomarker to evaluate the malignancy and the prognosis of glioma patients is unknown. In the present study, we performed immunohistochemical analysis to evaluate MSP58 protein expression in 158 specimens of human gliomas and

34 normal control brain tissues. Compared with the control tissues, MSP58 expression was not only significantly higher in the glioma tissues ($P < 0.05$), but also increased with the increasing pathological grade ($P < 0.001$). Furthermore, the Kaplan-Meier analysis showed that high expression of MSP58 could predict poor survival in glioma patients ($P < 0.001$). In the multivariate analysis, high expression of MSP58 was also an independent unfavorable prognostic factor for the overall survival in glioma patients ($P < 0.001$, hazard ratio, 8.177, 95 % CI 2.571-26.008). In conclusion, the increased expression of MSP58 is correlated with a higher malignant grade and poor prognosis in glioma patients. MSP58 is valuable both as an indicator of the malignancy of gliomas and as a prognostic factor for the clinical outcome of glioma patients.

[138]

TÍTULO / TITLE: - Predicting risk of cancer during HIV infection: the role of inflammatory and coagulation biomarkers.

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

REVISTA / JOURNAL: - AIDS. 2013 Jun 1;27(9):1433-41. doi: 10.1097/QAD.0b013e32835f6b0c.

●● Enlace al texto completo (gratis o de pago) [1097/QAD.0b013e32835f6b0c](#)

AUTORES / AUTHORS: - Borges AH; Silverberg MJ; Wentworth D; Grulich AE; Fatkenheuer G; Mitsuyasu R; Tambussi G; Sabin CA; Neaton JD; Lundgren JD

INSTITUCIÓN / INSTITUTION: - Department of Infectious Diseases, Rigshospitalet and Copenhagen HIV Programme, University of Copenhagen, Copenhagen, Denmark.

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RESUMEN / SUMMARY: - OBJECTIVE: To investigate the relationship between inflammatory [interleukin-6 (IL-6) and C-reactive protein (CRP)] and coagulation (D-dimer) biomarkers and cancer risk during HIV infection. DESIGN: A prospective cohort. METHODS: HIV-infected patients on continuous antiretroviral therapy (ART) in the control arms of three randomized trials (N=5023) were included in an analysis of predictors of cancer (any type, infection-related or infection-unrelated). Hazard ratios for IL-6, CRP and D-dimer levels (log₂-transformed) were calculated using Cox models stratified by trial and adjusted for demographics and CD4⁺ cell counts and adjusted also for all biomarkers simultaneously. To assess the possibility that biomarker levels were elevated at entry due to undiagnosed cancer, analyses were repeated excluding early cancer events (i.e. diagnosed during first 2 years of follow-up). RESULTS: During approximately 24,000 person-years of follow-up (PYFU), 172 patients developed cancer (70 infection-related; 102 infection-unrelated). The risk of developing cancer was associated with higher levels (per doubling) of IL-6 (hazard ratio 1.38, $P < 0.001$), CRP (hazard ratio 1.16, $P = 0.001$) and D-dimer (hazard ratio 1.17, $P = 0.03$). However, only IL-6 (hazard ratio 1.29, $P = 0.003$) remained associated with cancer risk when all biomarkers were considered simultaneously. Results for infection-related and

infection-unrelated cancers were similar to results for any cancer. Hazard ratios excluding 69 early cancer events were 1.31 (P=0.007), 1.14 (P=0.02) and 1.07 (P=0.49) for IL-6, CRP and D-dimer, respectively. CONCLUSION: Activated inflammation and coagulation pathways are associated with increased cancer risk during HIV infection. This association was stronger for IL-6 and persisted after excluding early cancer. Trials of interventions may be warranted to assess whether cancer risk can be reduced by lowering IL-6 levels in HIV-positive individuals.

[139]

TÍTULO / TITLE: - Eukaryotic translation initiation factor 4E (eIF4E) expression is associated with breast cancer tumor phenotype and predicts survival after anthracycline chemotherapy treatment.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Aug;141(1):79-88. doi: 10.1007/s10549-013-2671-2. Epub 2013 Aug 24.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2671-2](#)

AUTORES / AUTHORS: - Heikkinen T; Korpela T; Fagerholm R; Khan S; Aittomaki K; Heikkila P; Blomqvist C; Carpen O; Nevanlinna H

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Biomedicum Helsinki, P.O. Box 700, 00029, Helsinki, Finland, tuomas.heikkinen@helsinki.fi.

RESUMEN / SUMMARY: - Abnormal translation of mRNAs frequently occurring during carcinogenesis is among the mechanisms that can affect the expression of proteins involved in tumor development and progression. Eukaryotic initiation factor eIF4E is a key regulator of translation of many cancer-related transcripts and its expression is altered in various cancers and has been associated with worse survival. We determined the eIF4E protein levels using immunohistochemistry (IHC) in 1,233 breast tumors on tissue microarrays. We analyzed the effects of the IHC expression level on tumor characteristics and patient survival, also with stratification by adjuvant chemotherapy treatment. In 1,085 successfully stained tumors, high level of eIF4E protein expression was associated with features of aggressive tumor phenotype, namely grade, estrogen and progesterone receptor negativity, HER2 receptor positivity, and high expression of p53 and Ki67, and with triple negative subtype (p < 0.001). High eIF4E expression was associated with worse breast cancer-specific survival with a hazard ratio (HR) of 1.99 (95 % CI 1.32-3.00, p = 0.0008) and was in a multivariate analysis an independent prognostic factor. High eIF4E expression was associated with worse outcome also after detection of distant metastasis (HR = 1.88, 95 % CI 1.20-2.94, p = 0.0060). In the subgroup analysis the survival effect was strongest among patients treated with anthracycline chemotherapy (HR = 3.34, 95 % CI 1.72-6.48, p = 0.0002), whereas no such effect was seen among patients who had not

received anthracycline with significant difference in heterogeneity between the two groups ($p = 0.0358$). High expression of eIF4E is associated with adverse tumor characteristics and predicts poor breast cancer-specific survival. This effect is emphasized in patients treated with anthracycline chemotherapy. eIF4E as a treatment predictive factor warrants further studies.

[140]

TÍTULO / TITLE: - A novel isoform of the B cell tyrosine kinase BTK protects breast cancer cells from apoptosis.

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

REVISTA / JOURNAL: - Genes Chromosomes Cancer. 2013 Oct;52(10):961-75. doi: 10.1002/gcc.22091. Epub 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1002/gcc.22091](#)

AUTORES / AUTHORS: - Eifert C; Wang X; Kokabee L; Kourtidis A; Jain R; Gerdes MJ; Conklin DS

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, Gen*NY*Sis Center for Excellence in Cancer Genomics, University at Albany, Rensselaer, NY.

RESUMEN / SUMMARY: - Tyrosine kinases orchestrate key cellular signaling pathways and their dysregulation is often associated with cellular transformation. Several recent cases in which inhibitors of tyrosine kinases have been successfully used as anticancer agents have underscored the importance of this class of proteins in the development of targeted cancer therapies. We have carried out a large-scale loss-of-function analysis of the human tyrosine kinases using RNA interference to identify novel survival factors for breast cancer cells. In addition to kinases with known roles in breast and other cancers, we identified several kinases that were previously unknown to be required for breast cancer cell survival. The most surprising of these was the cytosolic, nonreceptor tyrosine kinase, Bruton's tyrosine kinase (BTK), which has been extensively studied in B cell development. Down regulation of this protein with RNAi or inhibition with pharmacological inhibitors causes apoptosis; overexpression inhibits apoptosis induced by Doxorubicin in breast cancer cells. Our results surprisingly show that BTK is expressed in several breast cancer cell lines and tumors. The predominant form of BTK found in tumor cells is transcribed from an alternative promoter and results in a protein with an amino-terminal extension. This alternate form of BTK is expressed at significantly higher levels in tumorigenic breast cells than in normal breast cells. Since this protein is a survival factor for these cells, it represents both a potential marker and novel therapeutic target for breast cancer. © 2013 Wiley Periodicals, Inc.

[141]

TÍTULO / TITLE: - Smoothened inhibition leads to decreased proliferation and induces apoptosis in esophageal adenocarcinoma cells.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Aug;31(7):480-9. doi: 10.3109/07357907.2013.820317.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.820317](#)

AUTORES / AUTHORS: - Zaidi AH; Komatsu Y; Kelly LA; Malhotra U; Rotoloni C; Kosovec JE; Zahoor H; Makielski R; Hoppo T; Jobe BA

INSTITUCIÓN / INSTITUTION: - Allegheny-Singer Research Institute, Allegheny Health Network, Pittsburgh, Pennsylvania 15224, USA.

RESUMEN / SUMMARY: - The Hedgehog (Hh) pathway is known to be active in Barrett's carcinogenesis. Therefore, we evaluated the efficacy and underlying mechanisms of inhibition of cancer cell growth by the smoothened (Smo) antagonist BMS-833923 in esophageal adenocarcinoma (EAC) cell lines. Cell proliferation and apoptosis were evaluated by flow cytometry, Western blotting, immunofluorescence, and quantitative reverse transcription polymerase chain reactions. Results showed that the Smo antagonist led to reduced Hh pathway activity, resulting in decreased cell proliferation and induction of apoptosis via the intrinsic pathway in the esophageal cancer cells. In conclusion, the Smo antagonist may have application as an EAC chemotherapeutic agent.

[142]

TÍTULO / TITLE: - Characteristics and prognosis analysis of additional chromosome abnormalities in newly diagnosed acute promyelocytic leukemia treated with arsenic trioxide as the front-line therapy.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug 16. pii: S0145-2126(13)00273-7. doi: 10.1016/j.leukres.2013.07.030.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.030](#)

AUTORES / AUTHORS: - Lou Y; Suo S; Tong H; Ye X; Wang Y; Chen Z; Qian W; Meng H; Mai W; Huang J; Tong Y; Jin J

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Institute of Hematology, The First Affiliated Hospital of Zhejiang University, School of Medicine, PR China.

RESUMEN / SUMMARY: - Currently, there are few studies that address the prognostic significance of baseline additional chromosomal abnormalities (ACAs) in newly diagnosed acute promyelocytic leukemia (APL) patients treated with arsenic trioxide (ATO) as the front-line therapy. A series of 271 consecutive APL patients has been cytogenetically investigated between 2004 and 2011 in our institution. The incidence of ACAs was 27% (46/172) in APL cases with t(15;17). Trisomy 8 was the most recurrent abnormality, accounting for 30% (14/46) of patients with ACAs, followed by

+21 (7%, 3/46) and -7/7q (7%, 3/46). Nine cases (14.1%) were found to have additional balanced translocation aberrations, most of them are new and non-recurrent. Treatment protocols consisted of all-trans retinoic acid (ATRA) and chemotherapy with or without the ATO therapy. Overall, patients with and without ACAs had similar complete remission (CR) rates (94% and 98%, respectively, P=0.344). With a median follow-up of 41 months, univariate analysis showed that ACAs did not show any prognostic significance in relapse-free survival (RFS) and overall survival (OS). In addition, ATO treatment was an independent favorable predictor for RFS. Thus, this data provides insights into cytogenetic features of APL, and suggests that ATO-based combination therapy improved RFS in de novo APL patients, while ACAs had no impact on prognosis.

[143]

TÍTULO / TITLE: - Phase I Study of GTI-2040, a Ribonucleotide Reductase Anti-Sense, with High Dose Cytarabine in Patients with Relapsed/Refractory Acute Myeloid Leukemia.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 10.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.838764](#)

AUTORES / AUTHORS: - Klisovic RB; Blum W; Liu Z; Xie Z; Kefauver C; Huynh L; Zwiebel JA; Devine SM; Byrd JC; Grever MR; Chan KK; Marcucci G

RESUMEN / SUMMARY: - ABSTRACT We hypothesized that GTI-2040, a 20-mer oligonucleotide complementary to the R2 subunit mRNA of ribonucleotide reductase, combined with high dose cytarabine (HiDAC) would result in enhanced cytotoxicity by favoring Ara-CTP DNA incorporation. In a Phase I dose escalation trial, adults (>= 60 years) with refractory or relapsed acute myeloid leukemia (AML) received daily HiDAC plus infusional GTI-2040. Using a novel assay, evidence of intracellular drug accumulation and target R2 downregulation were observed. GTI-2040/HiDAC can be administered safely. However, with no complete remissions observed, alternate doses and schedules may need to be investigated to achieve clinical activity in older AML patients.

[144]

TÍTULO / TITLE: - Increased expression of phosphorylated NBS1, a key molecule of the DNA damage response machinery, is an adverse prognostic factor in patients with de novo myelodysplastic syndromes.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Sep 5. pii: S0145-2126(13)00300-7. doi: 10.1016/j.leukres.2013.08.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.08.018](#)

AUTORES / AUTHORS: - Kefala M; Papageorgiou SG; Kontos CK; Economopoulou P; Tsanas A; Pappa V; Panayiotides IG; Gorgoulis VG; Patsouris E; Foukas PG

INSTITUCIÓN / INSTITUTION: - 2nd Department of Pathology, University of Athens Medical School, "Attikon" University Hospital, Chaidari, Greece.

RESUMEN / SUMMARY: - The expression of activated forms of key proteins of the DNA damage response machinery (pNBS1, pATM and gammaH2AX) was assessed by means of immunohistochemistry in bone marrow biopsies of 74 patients with de novo myelodysplastic syndromes (MDS) and compared with 15 cases of de novo acute myeloid leukemia (AML) and 20 with reactive bone marrow histology. Expression levels were significantly increased in both MDS and AML, compared to controls, being higher in high-risk than in low-risk MDS. Increased pNBS1 and gammaH2AX expression possessed a significant negative prognostic impact for overall survival in MDS patients, whereas pNBS1 was an independent marker of poor prognosis.

[145]

TÍTULO / TITLE: - Combination of vorinostat and low dose cytarabine for patients with azacitidine-refractory/relapsed high risk myelodysplastic syndromes.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug 13. pii: S0145-2126(13)00265-8. doi: 10.1016/j.leukres.2013.07.023.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.leukres.2013.07.023](#)

AUTORES / AUTHORS: - Prebet T; Braun T; Beyne-Rauzy O; Dreyfus F; Stamatoullas A; Wattel E; Ame S; Raffoux E; Delaunay J; Charbonnier A; Ades L; Fenaux P; Vey N

INSTITUCIÓN / INSTITUTION: - Hematology Department, Institut PAOLI-CALMETTES and Aix-Marseille Université, Marseille, France.

RESUMEN / SUMMARY: - Outcome of patients with myelodysplastic syndrome after azacitidine failure is poor. In this population, we combined cytarabine (10-20mg/m²/day 14 days) with vorinostat (400mg/day) for escalating durations (7 days, 10 days and 14 days), and starting on day 1 (concomitant arm) or on day 14 (sequential arm) following a 3+3 phase I design. 40 patients were treated. Dose limiting toxicities were all seen in sequential arm. The overall response rate was 15% with 4 responses in concomitant arm (ORR=25%). We conclude that this combination is tolerable and concomitant administration might be less toxic and have better therapeutic effect (clinicaltrials.gov NCT00776503).

[146]

TÍTULO / TITLE: - Inherited genetic susceptibility to breast cancer: the beginning of the end or the end of the beginning?

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

REVISTA / JOURNAL: - Am J Pathol. 2013 Oct;183(4):1038-51. doi: 10.1016/j.ajpath.2013.07.003. Epub 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1016/j.ajpath.2013.07.003](https://doi.org/10.1016/j.ajpath.2013.07.003)

AUTORES / AUTHORS: - Ghousaini M; Pharoah PD; Easton DF

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, United Kingdom. Electronic address: mg458@medschl.cam.ac.uk.

RESUMEN / SUMMARY: - Genome-wide association studies have identified 72 loci associated with breast cancer susceptibility. Seventeen of these are known to predispose to other cancers. High-penetrance susceptibility loci for breast cancer usually result from coding alterations, principally in genes involved in DNA repair, whereas almost all of the associations identified through genome-wide association studies are found in noncoding regions of the genome and are likely to involve regulation of genes in multiple pathways. However, the genes underlying most associations are not yet known. In this review, we summarize the findings from genome-wide association studies in breast cancer and describe the genes and mechanisms that are likely to be involved in the tumorigenesis process. We also discuss approaches to fine-scale mapping of susceptibility regions used to identify the likely causal variant(s) underlying the associations, a major challenge in genetic epidemiology. Finally, we discuss the potential impact of such findings on personalized medicine and future avenues for screening, prediction, and prevention programs.

[147]

TÍTULO / TITLE: - A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC).

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Oct;82(1):109-14. doi: 10.1016/j.lungcan.2013.07.003. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.07.003](https://doi.org/10.1016/j.lungcan.2013.07.003)

AUTORES / AUTHORS: - Goto K; Nishio M; Yamamoto N; Chikamori K; Hida T; Maemondo M; Katakami N; Kozuki T; Yoshioka H; Seto T; Fukuyama T; Tamura T

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan. Electronic address: kgoto@east.ncc.go.jp.

RESUMEN / SUMMARY: - INTRODUCTION: The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib is associated with survival benefits in patients with EGFR mutation-positive non-small-cell lung cancer (NSCLC). This phase II, single-arm study examined the efficacy and safety of first-line erlotinib in Japanese patients with EGFR mutation-positive NSCLC. METHODS: Eligible patients received erlotinib 150mg/day until disease progression or unacceptable toxicity. The primary endpoints

were progression-free survival (PFS) and safety. RESULTS: A high degree of concordance was observed between different mutation testing methodologies, suggesting feasibility of early, rapid detection of EGFR mutations. Median PFS was 11.8 months (95% confidence interval [CI]: 9.7-15.3) at data cut-off (1 June 2012) (n=102). Exon 19 deletions seemed to be associated with longer PFS compared with L858R mutations; T790M mutations were tentatively linked with shorter PFS. The safety profile was as expected: rash (any grade; 83%) and diarrhea (any grade; 81%) were most common. Six interstitial lung disease (ILD)-like cases were reported, and 5 were confirmed as ILD-like events by the extramural committee. Two patients died of treatment-related pneumonitis (JAPIC Clinical Trials Information number: Japic CTI-101085). CONCLUSION: Erlotinib should be considered for first-line treatment in this subset of Japanese patients, with close monitoring for ILD-like events.

[148]

TÍTULO / TITLE: - Identification of a 5-gene signature for clinical and prognostic prediction in gastric cancer patients upon microarray data.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):678. doi: 10.1007/s12032-013-0678-5. Epub 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0678-5](#)

AUTORES / AUTHORS: - Wang Z; Yan Z; Zhang B; Rao Z; Zhang Y; Liu J; Yu L; Zhao Y; Yang B; Wu T; Gao J

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Wuhan General Hospital of Guangzhou Command, People's Liberation Army, 627 Wuluo Road, Wuhan 430070, People's Republic of China.

RESUMEN / SUMMARY: - In this study, we aimed to investigate the clinical and prognostic value of a 5-gene expression signature model for gastric cancer patients upon microarray data. A total of 158 gastric cancer patients were selected, with 33 cases used for microarray analysis as training set and 125 cases for validation real-time quantitative polymerase chain reaction analysis as test set. Unsupervised clustering algorithms and supervised clustering algorithm were used to identify differentially expressed genes. Gene ontology analyses were used to determine functional prediction of gene biomarkers and receiver operating characteristic analyses to verify the specificity and sensitivity of the evaluation. Moreover, the correlation between clinicopathological characteristics and 5-gene expression was evaluated. The results showed that there were poor disease progression and clinic prognosis in the patients with proximal gastric cancer compared with distal gastric cancer, including differentiation grade ($P = 0.001$), depth of tumor invasion ($P < 0.01$), lymph node metastasis ($P < 0.01$), UICC stage ($P < 0.01$), and survival status ($P < 0.01$). Furthermore, a 5-gene signature, including cordon-bleu protein-like 1, damage-specific DNA binding

protein 1, BCL2-like 13, nuclear receptor coactivator-6, and F-box leucine-rich protein 11, was identified based on the combination of multiple bioinformatics algorithm. The expression of 5-gene signature (HR = 2.35; 95 % confidence interval 1.24-5.06; P = 0.026) and UICC stage (HR = 5.35; 95 % confidence interval 1.36-19.15; P = 0.032) was independent prognostic factors for overall survival in the survival multivariate analysis. Over-expression of the 5-gene signature in patients with proximal gastric cancer is strongly associated with disease progression and poor prognosis, suggesting that might be potential prognostic predictors in gastric cancer.

[149]

TÍTULO / TITLE: - Proapoptotic Peptide-Mediated Cancer Therapy Targeted to Cell Surface p32.

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

REVISTA / JOURNAL: - Mol Ther. 2013 Aug 20. doi: 10.1038/mt.2013.191.

●● [Enlace al texto completo \(gratis o de pago\) 1038/mt.2013.191](#)

AUTORES / AUTHORS: - Agemy L; Kotamraju VR; Friedmann-Morvinski D; Sharma S; Sugahara KN; Ruoslahti E

INSTITUCIÓN / INSTITUTION: - 1] Cancer Research Center, Sanford-Burnham Medical Research Institute, La Jolla, California, USA [2] Center for Nanomedicine and Department of Cell, Molecular and Developmental Biology, University of California, Santa Barbara, California, USA.

RESUMEN / SUMMARY: - Antiangiogenic therapy is a promising new treatment modality for cancer, but it generally produces only transient tumor regression. We have previously devised a tumor-targeted nanosystem, in which a pentapeptide, CGKRR, delivers a proapoptotic peptide into the mitochondria of tumor blood vessel endothelial cells and tumor cells. The treatment was highly effective in glioblastoma mouse models completely refractory to other antiangiogenic treatments. Here, we identify p32/gC1qR/HABP, a mitochondrial protein that is also expressed at the cell surface of activated (angiogenic) endothelial cells and tumor cells, as a receptor for the CGKRR peptide. The results demonstrate the ability of p32 to cause internalization of a payload bound to p32 into the cytoplasm. We also show that nardilysin, a protease capable of cleaving CGKRR, plays a role in the internalization of a p32-bound payload. As p32 is overexpressed and surface displayed in breast cancers, we studied the efficacy of the nanosystem in this cancer. We show highly significant treatment results in an orthotopic model of breast cancer. The specificity of cell surface p32 for tumor-associated cells, its ability to carry payloads to mitochondria, and the efficacy of the system in important types of cancer make the nanosystem a promising candidate for further development. *Molecular Therapy* (2013); doi:10.1038/mt.2013.191.

[150]

TÍTULO / TITLE: - Epigenome-wide DNA methylation landscape of melanoma progression to brain metastasis reveals aberrations on homeobox D cluster associated with prognosis.

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

REVISTA / JOURNAL: - Hum Mol Genet. 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1093/hmg/ddt420](#)

AUTORES / AUTHORS: - Marzese DM; Scolyer RA; Huynh JL; Huang SK; Hirose H; Chong KK; Kiyohara E; Wang J; Kawas NP; Donovan NC; Hata K; Wilmott JS; Murali R; Buckland ME; Shivalingam B; Thompson JF; Morton DL; Kelly DF; Hoon DS

INSTITUCIÓN / INSTITUTION: - Department of Molecular Oncology.

RESUMEN / SUMMARY: - Melanoma brain metastasis (MBM) represents a frequent complication of cutaneous melanoma. Despite aggressive multi-modality therapy, patients with MBM often have a survival rate of <1 year. Alteration in DNA methylation is a major hallmark of tumor progression and metastasis; however, it remains largely unexplored in MBM. In this study, we generated a comprehensive DNA methylation landscape through the use of genome-wide copy number, DNA methylation and gene expression data integrative analysis of melanoma progression to MBM. A progressive genome-wide demethylation in low CpG density and an increase in methylation level of CpG islands according to melanoma progression were observed. MBM-specific partially methylated domains (PMDs) affecting key brain developmental processes were identified. Differentially methylated CpG sites between MBM and lymph node metastasis (LNM) from patients with good prognosis were identified. Among the most significantly affected genes were the HOX family members. DNA methylation of HOXD9 gene promoter affected transcript and protein expression and was significantly higher in MBM than that in early stages. A MBM-specific PMD was identified in this region. Low methylation level of this region was associated with active HOXD9 expression, open chromatin and histone modifications associated with active transcription. Demethylating agent induced HOXD9 expression in melanoma cell lines. The clinical relevance of this finding was verified in an independent large cohort of melanomas (n = 145). Patients with HOXD9 hypermethylation in LNM had poorer disease-free and overall survival. This epigenome-wide study identified novel methylated genes with functional and clinical implications for MBM patients.

[151]

TÍTULO / TITLE: - PBMC expressed adiponectin mRNA is predictive of survival in patients with gastric cancer.

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

REVISTA / JOURNAL: - Clin Chem. [journals.uchicago.edu/](#) ●● Clinical Infectious Diseases: <> Lab Med. 2013 Aug 17:1-4. doi: 10.1515/cclm-2013-0453.

- Enlace al texto completo (gratuito o de pago) [1515/cclm-2013-0453](https://doi.org/10.1155/cclm-2013-0453)

AUTORES / AUTHORS: - Tsai JS; Lin MT; Wu MS; Huang KC; Lue BH; Lee LT; Chiu TY; Chen CH; Chen SC; Chuang LM; Chen CY

[152]

TÍTULO / TITLE: - Discovery of novel src homology region 2 domain-containing phosphatase 1 agonists from sorafenib for the treatment of hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Hepatology. 2013 Aug 2. doi: 10.1002/hep.26640.

- Enlace al texto completo (gratuito o de pago) [1002/hep.26640](https://doi.org/10.1002/hep.26640)

AUTORES / AUTHORS: - Tai WT; Shiau CW; Chen PJ; Chu PY; Huang HP; Liu CY; Huang JW; Chen KF

INSTITUCIÓN / INSTITUTION: - Department of Medical Research, National Taiwan University Hospital, Taipei, 10055, Taiwan; National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, Taipei, 10055, Taiwan.

RESUMEN / SUMMARY: - Sorafenib is the first approved targeted therapeutic reagent for hepatocellular carcinoma (HCC). Here, we report that Src homology region 2 (SH2) domain-containing phosphatase 1 (SHP-1) is a major target of sorafenib and generates a series of sorafenib derivatives to search for potent SHP-1 agonists that may act as better anti-HCC agents than sorafenib. Sorafenib increases SHP-1 activity by direct interaction and impairs the association between the N-SH2 domain and the catalytic protein tyrosine phosphatase domain of SHP-1. Deletion of the N-SH2 domain (dN1) or point mutation (D61A) of SHP-1 abolished the effect of sorafenib on SHP-1, phosphorylated signal transducer and activator of transcription 3 (p-STAT3), and apoptosis, suggesting that sorafenib may affect SHP-1 by triggering a conformational switch relieving its autoinhibition. Molecular docking of SHP-1/sorafenib complex confirmed our findings in HCC cells. Furthermore, novel sorafenib derivatives SC-43 and SC-40 displayed more-potent anti-HCC activity than sorafenib, as measured by enhanced SHP-1 activity, inhibition of p-STAT3, and induction of apoptosis. SC-43 induced substantial apoptosis in sorafenib-resistant cells and showed better survival benefits than sorafenib in orthotopic HCC tumors. Conclusion: In this study, we identified SHP-1 as a major target of sorafenib. SC-43 and SC-40, potent SHP-1 agonists, showed better anti-HCC effects than sorafenib in vitro and in vivo. Further clinical investigation is warranted. (Hepatology 2013;).

[153]

TÍTULO / TITLE: - TNFAIP8 as a predictor of metastasis and a novel prognostic biomarker in patients with epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17;109(6):1685-92. doi: 10.1038/bjc.2013.501. Epub 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.501](https://doi.org/10.1038/bjc.2013.501)

AUTORES / AUTHORS: - Liu T; Gao H; Chen X; Lou G; Gu L; Yang M; Xia B; Yin H

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, The Third Affiliated Hospital, Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - Background:Tumour necrosis factor-alpha-induced protein 8 (TNFAIP8) has been recently documented in various malignancies, but its role in epithelial ovarian cancer (EOC) remains unknown.Methods:Tumour necrosis factor-alpha-induced protein 8 expression was determined by real-time reverse transcription PCR and western blot analysis. Tumour tissues, consisting of serous, mucinous, endometrioid and clear cell histotypes, from 202 EOC patients (International Federation of Gynecologists and Obstetricians I-IV) who underwent primary cytoreduction were collected. Then, we examined the immunohistochemical expression of TNFAIP8 and evaluated its clinical significances.Results:Tumour necrosis factor-alpha-induced protein 8 overexpression was significantly associated with high histologic grade (P=0.005), large residual tumour size (P=0.014), recurrence (P=0.024) and response to chemotherapy (P<0.001). Multivariate analysis showed that TNFAIP8 overexpression was independently correlated with the presence of lymph node (odds ratio (OR): 4.129; 95% confidence interval (CI): 1.491-11.435; P=0.006) and intraperitoneal metastasis (OR: 2.209; 95% CI: 1.174-4.156; P=0.014). Moreover, results revealed that the status of TNFAIP8 expression was an independently prognostic factor for both cancer-specific survival (hazard ratio (HR): 1.852; 95% CI: 1.322-2.594; P<0.001) and disease-free survival (HR: 1.724; 95% CI: 1.235-2.407; P=0.001) in patients with EOC.Conclusion:The present data provide evidence that TNFAIP8 predicts EOC metastasis and poor survival, highlighting its potential function as a therapeutic target for EOCs.

[154]

TÍTULO / TITLE: - Prognostic value of ABO blood group in southern Chinese patients with established nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 10. doi: 10.1038/bjc.2013.559.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.559](https://doi.org/10.1038/bjc.2013.559)

AUTORES / AUTHORS: - Ouyang PY; Su Z; Mao YP; Liu Q; Xie FY

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, China.

RESUMEN / SUMMARY: - Background:ABO blood group is associated with aetiology of nasopharyngeal carcinoma (NPC); however, the effect of it on survival of patients

diagnosed with NPC has not been explored. Methods: We retrospectively analysed two cohorts of southern Chinese patients with WHO histological type III: intensity-modulated radiotherapy (IMRT) cohort, 924 patients; and conventional radiotherapy (CRT) cohort, 1193 patients. Associations of ABO blood group with survival were estimated using Cox regression. Results: In IMRT cohort, we observed significant associations of blood type A with overall survival (OS) and distant metastasis-free survival (DMFS), compared with type O, after adjusting for prognostic factors. Compared with non-A blood types (B, AB, and O), type A patients had significantly lower OS and DMFS (adjusted hazard ratio (HR)=1.49, 95% CI 1.03-2.17, P=0.036; HR=1.68, 95% CI 1.13-2.51, P=0.011, respectively); similar results were obtained in CRT cohort. Subgroup analyses of the entire population showed that lower OS conferred by blood type A was not significantly modified by age, smoking status, drinking status, immunoglobulin A against Epstein-Barr virus viral capsid antigen (VCA-IgA) titre, or chemotherapy; however, lower OS was not observed in female patients or patients with early clinical stage disease. Conclusion: ABO blood group is associated with survival in NPC; patients with blood type A had significantly lower OS and DMFS than patients with non-A blood types. British Journal of Cancer advance online publication, 10 September 2013; doi:10.1038/bjc.2013.559 www.bjcancer.com.

[155]

TÍTULO / TITLE: - Phase 2 Study of Pemetrexed Plus Carboplatin, or Pemetrexed Plus Cisplatin with Concurrent Radiation Therapy Followed by Pemetrexed Consolidation in Patients with Favorable-Prognosis Inoperable Stage IIIA/B Non-Small-Cell Lung Cancer.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [1097/JTO.0b013e3182a02546](https://doi.org/10.1097/JTO.0b013e3182a02546)

AUTORES / AUTHORS: - Choy H; Schwartzberg LS; Dakhil SR; Garon EB; Gerber DE; Choksi JK; Govindan R; Peng G; Koustenis A; Treat J; Obasaju C

INSTITUCIÓN / INSTITUTION: - *University of Texas Southwestern, Dallas, Texas; daggerACORN and West Clinic, Memphis, Tennessee; double daggerCancer Center of Kansas, Wichita, Kansas; section signUCLA/Translational Oncology Research International Network, Los Angeles, Los Angeles; | | Alamance Regional Medical Center, Burlington, North Carolina; paragraph signWashington University, St. Louis, Missouri; and #Lilly USA, LLC, Indianapolis, Indiana.

RESUMEN / SUMMARY: - INTRODUCTION:: There is no consensus chemotherapy regimen with concurrent radiotherapy (RT) for inoperable stage IIIA/B non-small-cell lung cancer. This trial evaluated pemetrexed with carboplatin (PCb) or cisplatin (PC) with concurrent RT followed by consolidation pemetrexed. METHODS:: In this open-label, noncomparative phase II trial, patients with inoperable stage IIIA/B non-small-cell lung cancer (initially all histologies, later restricted to nonsquamous) were randomized (1:1)

to PCb or PC with concurrent RT (64-68 Gy over days 1-45). Consolidation pemetrexed monotherapy was administered every 21 days for three cycles. Primary endpoint was 2-year overall survival (OS) rate. RESULTS:: From June 2007 to November 2009, 98 patients were enrolled (PCb: 46; PC: 52). The 2-year OS rate was PCb: 45.4% (95% confidence interval [CI], 29.5-60.0%); PC: 58.4% (95% CI, 42.6-71.3%), and in nonsquamous patients was PCb: 48.0% (95% CI, 29.0-64.8%); PC: 55.8% (95% CI, 38.0-70.3%). Median time to disease progression was PCb: 8.8 months (95% CI, 6.0-12.6 months); PC: 13.1 months (95% CI, 8.3-not evaluable [NE]). Median OS (months) was PCb: 18.7 (95% CI, 12.9-NE); PC: 27.0 (95% CI, 23.2-NE). The objective response rates (ORRs) were PCb: 52.2%; PC: 46.2%. Grade 4 treatment-related toxicities (% PCb/% PC) were: anemia, 0/1.9; neutropenia, 6.5/3.8; thrombocytopenia, 4.3/1.9; and esophagitis, 0/1.9. Most patients completed scheduled chemotherapy and RT during induction and consolidation phases. No drug-related deaths were reported during chemoradiotherapy. CONCLUSIONS:: Because of study design, efficacy comparisons cannot be made. However, both combinations with concurrent RT were active and well tolerated.

[156]

TÍTULO / TITLE: - Effect of the tyrosine kinase inhibitor nilotinib in patients with hypereosinophilic syndrome/chronic eosinophilic leukemia: analysis of the phase 2, open-label, single-arm A2101 study.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Sep 22.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1529-7](#)

AUTORES / AUTHORS: - Hochhaus A; le Coutre PD; Kantarjian HM; Baccarani M; Erben P; Reiter A; McCulloch T; Fan X; Novick S; Giles FJ

INSTITUCIÓN / INSTITUTION: - Abteilung Hamatologie/Onkologie, Universitätsklinikum Jena, Jena, Germany, andreas.hochhaus@med.uni-jena.de.

RESUMEN / SUMMARY: - PURPOSE: Hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia (CEL) are characterized by sustained overproduction of eosinophils and organ dysfunction. CEL involves the presence of clonal genetic markers, such as a fusion of FIP1-like 1 protein and platelet-derived growth factor receptor alpha (FIP1L1-PDGFRalpha, or F/P) or PDGFRalpha-activating mutations. METHODS: Sixteen patients with HES/CEL were enrolled in the phase 2 nilotinib registration trial (NCT00109707) and treated with nilotinib 400 mg twice daily. The median duration of treatment was 95 days (range 3-1,079). RESULTS: Twelve patients had HES: 1 achieved a complete hematologic response (CHR), 3 achieved stable disease, 3 had progressive disease, and 5 were not evaluable for response. Four patients had CEL: 2 with the F/P fusion and 2 with PDGFRalpha-activating mutations. Both patients with an F/P fusion achieved a CHR; 1 also achieved a complete molecular

response (CMR). Of the 2 patients with PDGFRalpha-activating mutations, 1 had stable disease and the other achieved CMR. At 24 months, overall survival in the HES group was 75.0 % (95 % CI 50.5-100.0) and no patients in the CEL group died. Median survival was not yet reached after a median follow-up of 32 months. The most common grade 3/4 hematologic laboratory abnormalities were lymphocytopenia (31.3 %) and neutropenia (25.0 %). The most common drug-related nonhematologic grade 3/4 adverse event was pruritus, which occurred in 2 patients (12.5 %). CONCLUSIONS: Nilotinib 400 mg twice daily was effective in some patients with HES/CEL regardless of F/P mutation status, and the safety profile was consistent with other nilotinib studies.

[157]

TÍTULO / TITLE: - Expression of osteoblast and osteoclast regulatory genes in the bone marrow microenvironment in multiple myeloma: only up-regulation of Wnt inhibitors SFRP3 and DKK1 is associated with lytic bone disease.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Aug 5.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.820288](#)

AUTORES / AUTHORS: - Kristensen IB; Christensen JH; Lyng MB; Moller MB; Pedersen L; Rasmussen LM; Ditzel HJ; Abildgaard N

INSTITUCIÓN / INSTITUTION: - Department of Hematology.

RESUMEN / SUMMARY: - Multiple myeloma (MM) lytic bone disease (LBD) is caused by osteoclast activation and osteoblast inhibition. RANK/RANKL/OPG play central roles in osteoclast activation and Wnt inhibitor DKK1 in osteoblast inhibition. The role of other Wnt inhibitors is less clear. We evaluated gene expression of osteoclast regulators (RANK, RANKL, OPG, TRAIL, MIP1A), Wnt inhibitors (DKK1, SFRP2, SFRP3, sclerostin, WIF1) and osteoblast transcription factors (RUNX2, osterix) by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) in the bone marrow (BM) microenvironment using snap-frozen BM biopsies, thereby achieving minimal post-sampling manipulation, and gene expression profiling (GEP) data, reflecting the in vivo situation. We analyzed 110 biopsies from newly diagnosed patients with MM and monoclonal gammopathy of unknown significance (MGUS) and healthy volunteers. LBD was evaluated using standard radiographs and the bone resorption marker CTX-1. Protein levels were evaluated by enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry. Among Wnt inhibitors, only SFRP3 and DKK1 were significantly overexpressed in advanced LBD, correlating with protein levels. SFRP3 correlated with CTX-1. Our findings support osteoblast inhibition as the driving force behind MM LBD.

[158]

TÍTULO / TITLE: - A high serum uric Acid level is associated with poor prognosis in patients with acute myeloid leukemia.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3947-51.

AUTORES / AUTHORS: - Yamauchi T; Negoro E; Lee S; Takai M; Matsuda Y; Takagi K; Kishi S; Tai K; Hosono N; Tasaki T; Ikegaya S; Inai K; Yoshida A; Urasaki Y; Iwasaki H; Ueda T

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Faculty of Medical Sciences, University of Fukui, 23 Shimoaizuki, Matsuoka, Eiheiji Fukui, 910-1193, Japan. tyamauch@u-fukui.ac.jp.

RESUMEN / SUMMARY: - Uric acid in serum (S-UA) is produced by the breakdown of the cellular nucleic acids of leukemia cells, and may be a marker of disease aggressiveness. S-UA levels were examined for association with clinical outcomes in patients with acute myeloid leukemia (AML). Fifty-six patients with AML admitted to our Institution were evaluated retrospectively. The median S-UA level at diagnosis was 5.0 mg/dl (range 2-13.8 mg/dl). The S-UA levels did not correlate with peripheral lactate dehydrogenase, peripheral white blood cell counts, or peripheral blast counts, and were not proportional to bone marrow blast counts or marrow cellularity. The S-UA levels in the patients who achieved complete remission were slightly lower than those in those who did not. S-UA levels less than, or equal to the median (5.0 mg/dl) were significantly associated with better prognoses, compared with S-UA levels greater than 5.0 mg/dl. Thus, the S-UA level may predict the prognosis of AML, and is a versatile and cost-effective test for such a purpose.

[159]

TÍTULO / TITLE: - Is Letrozole needed for controlled ovarian stimulation in patients with estrogen receptor-positive breast cancer?

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

REVISTA / JOURNAL: - Gynecol Endocrinol. 2013 Nov;29(11):993-996. Epub 2013 Sep 3.

●● [Enlace al texto completo \(gratis o de pago\) 3109/09513590.2013.819083](#)

AUTORES / AUTHORS: - Revelli A; Porcu E; Levi Setti PE; Delle Piane L; Merlo DF; Anserini P

INSTITUCIÓN / INSTITUTION: - Physiopathology of Reproduction and IVF Unit, Department of Surgical Sciences, S. Anna Hospital, University of Torino, Torino, Italy.

RESUMEN / SUMMARY: - Abstract Objective: To assess the advantages and disadvantages of using Letrozole for controlled ovarian stimulation (COH) in young patients with estrogen receptor-positive (ER+) breast cancer, wishing to cryopreserve oocytes. Design: Retrospective cohort analysis. Setting: Sixteen Italian units for reproductive medicine and in vitro fertilization. Methods: Data of 50 ER+ breast cancer patients undergoing COH to cryopreserve oocytes before gonadotoxic chemotherapy with a Letrozole plus gonadotropins (Le+Gn) protocol were compared with those of 25 young

women with ER- breast cancer, submitted to COH using a protocol with gonadotropins alone (Gn-only). Results: The Le+Gn protocol implied a significantly lower total Gn consumption and allowed to maintain significantly lower circulating E2 levels at all checkpoints throughout stimulation (peak E2 value 446 +/- 357 versus 1553 +/- 908 pg/ml, respectively; p = 0.001). On the other side, the Le+Gn protocol allowed a significantly lower yield of oocytes available for cryostorage (6.6 +/- 3.5 versus 8 +/- 5, respectively; p = 0.038). Conclusions: In breast cancer patients, the association of Letrozole to Gn significantly reduces the number of oocytes available for cryostorage in comparison with the use of Gn alone. On the other side, it is associated with significantly lower E2 levels during the whole stimulation cycle, a safety issue that has been traditionally considered advantageous in case of ER+ cancers.

[160]

TÍTULO / TITLE: - Overexpression of CENP-H as a novel prognostic biomarker for human hepatocellular carcinoma progression and patient survival.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2238-44. doi: 10.3892/or.2013.2675. Epub 2013 Aug 20.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2675](#)

AUTORES / AUTHORS: - Lu G; Shan T; He S; Ren M; Zhu M; Hu Y; Lu X; Zhang D

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, First Affiliated Hospital of the Medical College, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, P.R. China.

RESUMEN / SUMMARY: - Centromere protein H (CENP-H) has been shown to be significantly upregulated in many types of cancers and is associated with disrupted cell cycle regulation, cell proliferation and genetic instability. The aim of the present study was to explore the expression and localization of CENP-H in hepatocellular carcinoma (HCC) and determine whether its overexpression is a prognostic biomarker for HCC. Reverse transcription-polymerase chain reaction (pcr), real-time qPCR and western blotting were used to compare CENP-H expression at the mRNA and protein levels in HCC samples and corresponding adjacent non-cancerous samples. CENP-H protein levels were determined in 60 paired paraffin-embedded HCC tissues using immunohistochemistry (IHC), and the correlation with clinicopathological features and patient prognosis was analyzed. In addition, an immunofluorescence assay was performed to test the expression and localization of CENP-H protein in HCC cells. Results showed that levels of CENP-H mRNA and protein were higher in HCC samples than in the corresponding adjacent non-cancerous samples. In 60 paired paraffin-embedded tissues, CENP-H was upregulated in the HCC samples (38/60, 63.3%) relative to the adjacent non-cancerous samples (21/60, 35%, P=0.003), and a higher level of upregulation was associated with tumor size (P=0.032); higher histological grade (P=0.001); more advanced TNM stage (P=0.002) and Chinese clinical stage

($P=0.008$); and poorer prognosis. In addition, consistent with the results of IHC, the immunofluorescence assay showed that CENP-H was localized in the nucleus of Hep3B cells. CENP-H was overexpressed in HCC, and its level of upregulation was an independent prognostic indicator, suggesting that CENP-H may be an effective therapeutic strategy for the treatment of HCC.

[161]

TÍTULO / TITLE: - Zebularine induces chemosensitization to methotrexate and efficiently decreases AhR gene methylation in childhood acute lymphoblastic leukemia cells.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Sep 18.

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

[1097/CAD.0000000000000028](#)

AUTORES / AUTHORS: - Andrade AF; Borges KS; Castro-Gamero AM; Silveira VS; Suazo VK; Oliveira JC; Moreno DA; de Paula Queiroz RG; Scrideli CA; Tone LG

INSTITUCIÓN / INSTITUTION: - Departments of aGenetics bPediatrics, Ribeirao Preto Medical School, University of Sao Paulo (USP), Ribeirao Preto, SP, Brazil.

RESUMEN / SUMMARY: - Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy in childhood. Despite the advances in treatment, about 20% of patients relapse and/or die, indicating the need for different therapies for this group. Zebularine (ZB) is a potent DNA methyltransferase (DNMT) inhibitor and has been associated with gene demethylation and enhancement of tumor chemosensitivity. This study aimed to evaluate the effects of ZB, alone or combined with chemotherapeutics (methotrexate and vincristine), on childhood ALL cell lines. Cell proliferation, apoptosis, and clonogenic capacity were studied in Jurkat and ReH cell lines. Bisulfite modification, followed by methylation-specific PCR was carried out to evaluate aryl hydrocarbon receptor (AhR) methylation status. Gene expression of DNMT1, DNMT3a, DNMT3b, and AhR was assessed using qRT-PCR. Both cell cultures were sensitive to ZB, showing a dose-dependent and time-dependent response ($P<0.05$). ZB induced apoptosis and decreased clonogenic capacity in both cell lines. Combination with methotrexate resulted in a strong synergistic effect, whereas combination with vincristine led to an antagonistic response in both cell lines. ZB treatment decreased gene expression of the three DNMTs and induced AhR gene promoter demethylation and its re-expression. These results indicate that ZB may be a promising drug for the adjuvant treatment of ALL, mainly when combined with methotrexate.

[162]

TÍTULO / TITLE: - Applicability of gene expression profile of childhood acute lymphoblastic leukemia at diagnosis and at the end of the induction phase of chemotherapy at a cancer hospital in the state of Goiás (Brazil).

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1192-2](#)

AUTORES / AUTHORS: - Minasi LB; Godoy FR; E Silva DD; Vieira TC; da Silva CC; da Cruz AD

INSTITUCIÓN / INSTITUTION: - Programa de Pos-Graduacao Stricto Sensu em Biologia, Instituto de Ciencias Biologicas, Universidade Federal de Goiás, Goiania, Goiás, Brazil, lysabernardes@yahoo.com.br.

RESUMEN / SUMMARY: - The present study compared the gene expression pattern of some previously described genes at the time of diagnosis and after induction chemotherapy for childhood acute lymphoblastic leukemia (ALL) in patients submitted to Brazilian Childhood Leukemia Treatment Group (GBTLI) ALL-99 Protocol. Samples were obtained at the time of diagnosis from 16 patients with ALL and on the 28th day of induction chemotherapy the bone marrow samples were obtained from 12 children. The genes expression profiles in diagnostic and induction samples were analyzed by array-based qPCR and then related to the clinical and biological prognostic factors. The results showed significant associations ($p \leq 0.05$) between gender and immunophenotype, immunophenotype and age, immunophenotype and risk group, presence of CD10 and RUNX1 expression, risk group, and immunophenotype. A significant positive correlation was observed between the expression levels of BAX and BCL2. There was a significant difference ($p = 0.008$) between the gene expression pattern at the time of diagnosis and after induction chemotherapy. The expression pattern of these genes after the induction phase of treatment approached the expression profile of the control group, indicating a good induction response in children treated according to the GBTLI ALL-99 protocol. The findings of the current research could be routinely useful for clinical practice and could assist in the discovery phase of medical applications.

[163]

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. 2013 Sep 20. doi: 10.4149/neo_2014_010.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2014_010](#)

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 amean 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>Apolymorphism in the ATM gene or single TGFB1 polymorphisms and late toxicity. TGFB1 compound homozygosity (-1552delAGG, -509C>T, L10P) was asignificant 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.

[164]

TÍTULO / TITLE: - HER2-overexpressing breast cancer: FDG uptake after two cycles of chemotherapy predicts the outcome of neoadjuvant treatment.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1157-64. doi: 10.1038/bjc.2013.469. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.469](#)

AUTORES / AUTHORS: - Groheux D; Giacchetti S; Hatt M; Marty M; Vercellino L; de Roquancourt A; Cuvier C; Coussy F; Espie M; Hindie E

INSTITUCIÓN / INSTITUTION: - 1] Nuclear Medicine, Saint-Louis Hospital, 1 avenue Claude Vellefaux, Paris 75475, France [2] B2T, Doctoral School, IUH, University of Paris VII, Paris, France.

RESUMEN / SUMMARY: - Background:Pathologic complete response (pCR) to neoadjuvant treatment (NAT) is associated with improved survival of patients with HER2+ breast cancer. We investigated the ability of interim positron emission tomography (PET) regarding early prediction of pathology outcomes.Methods:During 61 months, consecutive patients with locally advanced or large HER2+ breast cancer patients without distant metastases were included. All patients received NAT with four cycles of epirubicin+cyclophosphamide, followed by four cycles of docetaxel+trastuzumab. (18)F-fluorodeoxyglucose ((18)F-FDG)-PET/computed tomography (CT) was performed at baseline (PET1) and after two cycles of chemotherapy (PET2). Maximum standardised uptake values were measured in the primary tumour as well as in the axillary lymph nodes. The correlation between pathologic response and SUV parameters (SUVmax at PET1, PET2 and DeltaSUVmax)

was examined with the t-test. The predictive performance regarding the identification of non-responders was evaluated using receiver operating characteristics (ROC) analysis. Results: Thirty women were prospectively included and 60 PET/CT examination performed. At baseline, 22 patients had PET+ axilla and in nine of them (18)F-FDG uptake was higher than in the primary tumour. At surgery, 14 patients (47%) showed residual tumour (non-pCR), whereas 16 (53%) reached pCR. Best prediction was obtained when considering the absolute residual SUVmax value at PET2 (AUC=0.91) vs 0.67 for SUVmax at PET1 and 0.86 for DeltaSUVmax. The risk of non-pCR was 92.3% in patients with any site of residual uptake >3 at PET2, no matter whether in breast or axilla, vs 11.8% in patients with uptake <=3 (P=0.0001). The sensitivity, specificity, PPV, NPV and overall accuracy of this cutoff were, respectively: 85.7%, 93.8%, 92.3%, 88.2% and 90%. Conclusion: The level of residual (18)F-FDG uptake after two cycles of chemotherapy predicts residual disease at completion of NAT with chemotherapy+trastuzumab with high accuracy. Because many innovative therapeutic strategies are now available (e.g., addition of a second HER2-directed therapy or an antiangiogenic), early prediction of poor response is critical.

[165]

TÍTULO / TITLE: - Vascular endothelial growth factor C expression is closely correlated with lymph node recurrence and poor prognosis in patients with early stage cervical cancer.

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

REVISTA / JOURNAL: - J Int Med Res. 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1177/0300060513493038](#)

AUTORES / AUTHORS: - Demei M; Xiangxin L; Yongping X; Yongxia Y; Yunhai Y; Lin Z

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynaecology, The Second Hospital of Shandong University, Jinan, Shandong, China.

RESUMEN / SUMMARY: - OBJECTIVES: To detect vascular endothelial growth factor (VEGF)-C mRNA expression in surgically resected tissues of 'pathologic N0' (pN0) cervical cancer; to investigate the relevance of VEGF-C mRNA expression to clinicopathological factors, lymph node recurrence and prognosis in early stage cervical cancer. METHODS: Patients with pN0 cervical cancer who successfully underwent radical hysterectomy with bilateral adnexectomy and bilateral pelvic lymphadenectomy were enrolled sequentially into this retrospective study. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to detect VEGF-C mRNA. RESULTS: Seventy-eight patients entered the study. VEGF-C mRNA was detected in 35 (44.87%) patients and was significantly correlated with tumour differentiation. VEGF-C mRNA expression was significantly associated with lymph node recurrence and poor overall survival 5 years after surgery. Multivariate analysis confirmed that VEGF-C mRNA expression was an independent predictor for lymph

node recurrence and unfavourable overall survival. CONCLUSIONS: These findings indicate that detection of VEGF-C mRNA has clinical potential as a predictor for identifying patients with pN0 cervical cancer at high risk of lymph node recurrence and poor prognosis.

[166]

TÍTULO / TITLE: - Pain and health-related quality of life in patients with advanced solid tumours and bone metastases: integrated results from three randomized, double-blind studies of denosumab and zoledronic acid.

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

REVISTA / JOURNAL: - Support Care Cancer. 2013 Aug 22.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00520-013-1932-2](#)

AUTORES / AUTHORS: - von Moos R; Body JJ; Egerdie B; Stopeck A; Brown JE; Damyanov D; Fallowfield LJ; Marx G; Cleeland CS; Patrick DL; Palazzo FG; Qian Y; Braun A; Chung K

INSTITUCIÓN / INSTITUTION: - Kantonsspital Graubunden, Loestrasse 170, 7000, Chur, Switzerland, Roger.vonmoos@ksgr.ch.

RESUMEN / SUMMARY: - PURPOSE: This analysis evaluated patient-reported outcomes and analgesic use in patients with bone metastases from solid tumours across three comparative studies of denosumab and zoledronic acid. METHODS: Pooled data were analysed from three identically designed double-blind phase III studies comparing subcutaneous denosumab 120 mg with intravenous zoledronic acid 4 mg monthly in patients with bone metastases from breast cancer (n = 2,046), castration-resistant prostate cancer (n = 1,901) or other solid tumours (n = 1,597). Pain severity, pain interference, health-related quality of life and analgesic use were quantified. RESULTS: At baseline, approximately half of patients had no/mild pain (53 % [1,386/2,620] denosumab; 50 % [1,297/2,578] zoledronic acid). Denosumab delayed onset of moderate/severe pain by 1.8 months (median, 6.5 vs 4.7 months; hazard ratio, 0.83; 95 % CI, 0.76-0.92; p < 0.001; 17 % risk reduction) and clinically meaningful increases in overall pain interference by 2.6 months (median, 10.3 vs 7.7 months; hazard ratio, 0.83; 95 % CI, 0.75-0.92; p < 0.001; 17 % risk reduction) compared with zoledronic acid. Strong opioid use and worsening of health-related quality of life were less common with denosumab. CONCLUSIONS: Across three large studies of patients with advanced solid tumours and bone metastases, denosumab prevented progression of pain severity and pain interference more effectively than zoledronic acid.

[167]

TÍTULO / TITLE: - Treatment with cyclophosphamide, vindesine, cytarabine, dexamethasone, and bleomycin in patients with relapsed/refractory diffuse large B cell lymphoma.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.848984](#)

AUTORES / AUTHORS: - Li M; Li Y; Yin Q; Mi R; Chen L; Du J; Wei X

RESUMEN / SUMMARY: - Abstract Several chemotherapy regimens have been used as second-line therapies for relapsed and refractory diffuse large B cell lymphoma (DLBCL); none have emerged as a preferred regimen. This retrospective study aimed to identify a regimen with high efficacy and low toxicity for patients with relapsed and refractory DLBCL. Fifty-eight patients diagnosed with relapsed or refractory DLBCL were included in the study. Patients were treated with cyclophosphamide, vindesine, cytarabine, dexamethasone, and bleomycin (COAD-B). The overall response rate (ORR) was 70.7%, and the median remission duration was 13 months (3-48 months). The 1-, 2-, and 4-year overall survival rates were 62.4%, 45.7%, and 34.6%, respectively. The 1-, 2-, and 4-year progression-free survival rates were 50.0%, 36.7%, and 20.7%, respectively. The responses of patients with relapsed DLBCL to COAD-B were significantly better than those of patients with refractory DLBCL (P=0.005). The main adverse reaction of patients was myelosuppression. Our data indicate that COAD-B should be used in treatment of patients with relapsed DLBCL.

[168]

TÍTULO / TITLE: - Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population.

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

REVISTA / JOURNAL: - Lancet Oncol. 2013 Oct;14(11):1067-1076. doi: 10.1016/S1470-2045(13)70387-5. Epub 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1016/S1470-2045\(13\)70387-5](#)

AUTORES / AUTHORS: - Sgroi DC; Sestak I; Cuzick J; Zhang Y; Schnabel CA; Schroeder B; Erlander MG; Dunbier A; Sidhu K; Lopez-Knowles E; Goss PE; Dowsett M

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RESUMEN / SUMMARY: - BACKGROUND: Biomarkers to improve the risk-benefit of extended adjuvant endocrine therapy for late recurrence in patients with oestrogen-receptor-positive breast cancer would be clinically valuable. We compared the prognostic ability of the breast-cancer index (BCI) assay, 21-gene recurrence score (Oncotype DX), and an immunohistochemical prognostic model (IHC4) for both early and late recurrence in patients with oestrogen-receptor-positive, node-negative (N0) disease who took part in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) clinical trial. METHODS: In this prospective comparison study, we obtained archival

tumour blocks from the TransATAC tissue bank from all postmenopausal patients with oestrogen-receptor-positive breast cancer from whom the 21-gene recurrence score and IHC4 values had already been derived. We did BCI analysis in matched samples with sufficient residual RNA using two BCI models-cubic (BCI-C) and linear (BCI-L)-using previously validated cutoffs. We assessed prognostic ability of BCI for distant recurrence over 10 years (the primary endpoint) and compared it with that of the 21-gene recurrence score and IHC4. We also tested the ability of the assays to predict early (0-5 years) and late (5-10 years) distant recurrence. To assess the ability of the biomarkers to predict recurrence beyond standard clinicopathological variables, we calculated the change in the likelihood-ratio chi2 (LR-Deltachi2) from Cox proportional hazards models. FINDINGS: Suitable tissue was available from 665 patients with oestrogen-receptor-positive, NO breast cancer for BCI analysis. The primary analysis showed significant differences in risk of distant recurrence over 10 years in the categorical BCI-C risk groups ($p < 0.0001$) with 6.8% (95% CI 4.4-10.0) of patients in the low-risk group, 17.3% (12.0-24.7) in the intermediate group, and 22.2% (15.3-31.5) in the high-risk group having distant recurrence. The secondary analysis showed that BCI-L was a much stronger predictor for overall (0-10 year) distant recurrence compared with BCI-C (interquartile HR 2.30 [95% CI 1.62-3.27]; LR-Deltachi2=22.69; $p < 0.0001$). When compared with BCI-L, the 21-gene recurrence score was less predictive (HR 1.48 [95% CI 1.22-1.78]; LR-Deltachi2=13.68; $p = 0.0002$) and IHC4 was similar (HR 1.69 [95% CI 1.51-2.56]; LR-Deltachi2=22.83; $p < 0.0001$). All further analyses were done with the BCI-L model. In a multivariable analysis, all assays had significant prognostic ability for early distant recurrence (BCI-L HR 2.77 [95% CI 1.63-4.70], LR-Deltachi2=15.42, $p < 0.0001$; 21-gene recurrence score HR 1.80 [1.42-2.29], LR-Deltachi2=18.48, $p < 0.0001$; IHC4 HR 2.90 [2.01-4.18], LR-Deltachi2=29.14, $p < 0.0001$); however, only BCI-L was significant for late distant recurrence (BCI-L HR 1.95 [95% CI 1.22-3.14], LR-Deltachi2=7.97, $p = 0.0048$; 21-gene recurrence score HR 1.13 [0.82-1.56], LR-Deltachi2=0.48, $p = 0.47$; IHC4 HR 1.30 [0.88-1.94], LR-Deltachi2=1.59, $p = 0.20$). INTERPRETATION: BCI-L was the only significant prognostic test for risk of both early and late distant recurrence and identified two risk populations for each timeframe. It could help to identify patients at high risk for late distant recurrence who might benefit from extended endocrine or other therapy. FUNDING: Avon Foundation, National Institutes of Health, Breast Cancer Foundation, US Department of Defense Breast Cancer Research Program, Susan G Komen for the Cure, Breakthrough Breast Cancer through the Mary-Jean Mitchell Green Foundation, AstraZeneca, Cancer Research UK, and the National Institute for Health Research Biomedical Research Centre at the Royal Marsden (London, UK).

TÍTULO / TITLE: - Different effects of three interferons L on Toll-like receptor-related gene expression in HepG2 cells.

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

REVISTA / JOURNAL: - Cytokine. 2013 Sep 13. pii: S1043-4666(13)00673-X. doi: 10.1016/j.cyto.2013.08.010.

●● Enlace al texto completo (gratis o de pago) [1016/j.cyto.2013.08.010](#)

AUTORES / AUTHORS: - Kanda T; Jiang X; Nakamoto S; Nakamura M; Miyamura T; Wu S; Yokosuka O

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RESUMEN / SUMMARY: - IFNL1 (IL29), IFNL2 (IL28A) and IFNL3 (IL28B) might play important roles in anti-viral defense. IFNL3 genotypes have been shown to be associated with hepatitis C spontaneous and treatment-induced viral clearance. The effects of IFNL1, IFNL2 and IFNL3 on innate immunity including Toll-like receptor (TLR)-related pathway in human hepatocytes were examined. After G418 screening, we established the human hepatoma stable cell lines HepG2-IL28A, HepG2-IL28B, and HepG2-IL29, expressing IFNL2, IFNL3, and IFNL1 in conditioned medium, respectively, and a control cell line, HepG2-pcDNA3.1. We performed real-time RT-PCR to investigate 84 Toll-like receptor-related gene expressions in triplicate and, using ddCt methods, compared these gene expressions in each cell line. IFNL2, IFNL3 and IFNL1 were respectively detected by ELISA in HepG2-IL28A, HepG2-IL28B and HepG2-IL29. Compared to HepG2-pcDNA3.1 cells, 17 (20.2%), 11 (13.0%) and 16 genes (19.0%) were up-regulated 1.5-fold or more ($p < 0.05$); 10 (11.9%), 2 (2.3%) and 10 genes (11.9%) were 1.5-fold or more down-regulated ($p < 0.05$) in HepG2-IL28A, HepG2-IL28B and HepG2-IL29, respectively. EIF2AK2 and SARM1 were up-regulated among all cells. Of interest, TLR3, TLR4 and related molecules CXCL10 (IP10), IL6, EIF2K2, IFNB1, and IRF1, important genes in the progression of HCV-related pathogenesis and antiviral activities against HCV, in HepG2-IL28B, presented different profiles from those of HepG2-IL28A and HepG2-IL29. IFNL3 induces interferon-stimulated genes (ISGs) that are reportedly associated with the progression of HCV-related pathogenesis and antiviral activities against HCV. IFNL is a powerful modulator of innate immune response and it is supposed that the 3 IFNLs may play different roles in the antiviral activity against HBV and HCV.

[170]

TÍTULO / TITLE: - EUTOS score predicts long-term outcome but not optimal response to imatinib in patients with chronic myeloid leukaemia.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug 11. pii: S0145-2126(13)00280-4. doi: 10.1016/j.leukres.2013.07.037.

●● Enlace al texto completo (gratis o de pago) 1016/j.leukres.2013.07.037

AUTORES / AUTHORS: - Tiribelli M; Bonifacio M; Calistri E; Binotto G; Maino E; Marin L; Guardalben E; Branca A; Gherlinzoni F; Semenzato G; Sancetta R; Pizzolo G; Fanin R

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Bone Marrow Transplantation, Azienda Ospedaliero - Universitaria di Udine, Italy. Electronic address: mario.tiribelli@uniud.it.

RESUMEN / SUMMARY: - To test the recently developed EUTOS score in predicting optimal response to imatinib and the long-term outcome, 265 patients with early chronic phase chronic myeloid leukaemia treated with standard dose imatinib were analysed. Achievement of optimal response endpoints were higher in low-risk patients, though the difference was not statistically significant: PCyR at 6th month 86% vs 67% (p=0.06), CCyR at 12th month 80% vs 63% (p=0.09), MMR at 18th month 61% vs 36% (p=0.11). However, EUTOS score was predictive for the long-term response. With a median follow-up of 61 months, 53% high-risk patients experienced imatinib failure, compared to 23% in the low-risk group (p=0.013). Among high-risk patients, 4/17 (23%) progressed to accelerated/blastic phase or died, compared to 11/248 (5%) low-risk patients, with 5-year progression-free survival rates of 84+/-10% and 96+/-1%, respectively (p=0.04). Our data confirm that EUTOS score envisions the long-term outcome of imatinib therapy.

[171]

TÍTULO / TITLE: - Response to dasatinib in a patient with SQCC of the lung harboring a discoid-receptor-2 and synchronous chronic myelogenous leukemia.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Oct;82(1):171-2. doi: 10.1016/j.lungcan.2013.07.004. Epub 2013 Aug 9.

●● Enlace al texto completo (gratis o de pago) 1016/j.lungcan.2013.07.004

AUTORES / AUTHORS: - Pitini V; Arrigo C; Di Mirto C; Mondello P; Altavilla G

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University of Messina, Italy. Electronic address: vpitini@unime.it.

RESUMEN / SUMMARY: - We report a patient with squamous cell carcinoma (SQCC) of the lung and a discoid-receptor-2 (DDR2) kinase domain mutation that responded to dasatinib treatment. Our case report is consistent with previous publications suggesting that DDR2 mutation may confer sensitivity to dasatinib.

[172]

TÍTULO / TITLE: - miR-137 regulates the constitutive androstane receptor and modulates doxorubicin sensitivity in parental and doxorubicin-resistant neuroblastoma cells.

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

REVISTA / JOURNAL: - Oncogene. 2013 Aug 12. doi: 10.1038/onc.2013.330.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.330](#)

AUTORES / AUTHORS: - Takwi AA; Wang YM; Wu J; Michaelis M; Cinatl J; Chen T

INSTITUCIÓN / INSTITUTION: - Department of Chemical Biology and Therapeutics, St Jude Children's Research Hospital, Memphis, TN, USA.

RESUMEN / SUMMARY: - Chemotherapy is the most common treatment for cancer. However, multidrug resistance (MDR) remains a major obstacle to effective chemotherapy, limiting the efficacy of both conventional chemotherapeutic and novel biologic agents. The constitutive androstane receptor (CAR), a xenosensor, is a key regulator of MDR. It functions in xenobiotic detoxification by regulating the expression of phase I drug-metabolizing enzymes and ATP-binding cassette (ABC) transporters, whose overexpression in cancers and whose role in drug resistance make them potential therapeutic targets for reducing MDR. MicroRNAs (miRNAs) are endogenous negative regulators of gene expression and have been implicated in most cellular processes, including drug resistance. Here, we report the inversely related expression of miR-137 and CAR in parental and doxorubicin-resistant neuroblastoma cells, wherein miR-137 is downregulated in resistant cells. miR-137 overexpression resulted in downregulation of CAR protein and mRNA (via mRNA degradation); it sensitized doxorubicin-resistant cells to doxorubicin (as shown by reduced proliferation, increased apoptosis and increased G2-phase cell cycle arrest) and reduced the in vivo growth rate of neuroblastoma xenografts. We observed similar results in cellular models of hepatocellular and colon cancers, indicating that the doxorubicin-sensitizing effect of miR-137 is not tumor type-specific. Finally, we show for the first time a negative feedback loop whereby miR-137 downregulates CAR expression and CAR downregulates miR-137 expression. Hypermethylation of the miR-137 promoter and negative regulation of miR-137 by CAR contribute in part to reduced miR-137 expression and increased CAR and MDR1 expression in doxorubicin-resistant neuroblastoma cells. These findings demonstrate that miR-137 is a crucial regulator of cancer response to doxorubicin treatment, and they identify miR-137 as a highly promising target to reduce CAR-driven doxorubicin resistance. Oncogene advance online publication, 12 August 2013; doi:10.1038/onc.2013.330.

[173]

TÍTULO / TITLE: - Adhesion of ZAP-70+ chronic lymphocytic leukemia cells to stromal cells is enhanced by cytokines and blocked by inhibitors of the PI3-kinase pathway.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug 9. pii: S0145-2126(13)00282-8. doi: 10.1016/j.leukres.2013.08.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.08.001](https://doi.org/10.1016/j.leukres.2013.08.001)

AUTORES / AUTHORS: - Lafarge ST; Johnston JB; Gibson SB; Marshall AJ

INSTITUCIÓN / INSTITUTION: - University of Manitoba, Department of Immunology, Winnipeg, MB, Canada; Cancercare Manitoba, Manitoba Institute of Cell Biology, Winnipeg, MB, Canada.

RESUMEN / SUMMARY: - CLL cell survival and proliferation is enhanced through direct contact with supporting cells present in lymphoid tissues. PI3Ks are critical signal transduction enzymes controlling B cell survival and activation. PI3K inhibitors have entered clinical trials and show promising therapeutic activity; however, it is unclear whether PI3K inhibitor drugs differentially affect ZAP-70 positive versus negative CLL cells or target specific microenvironmental interactions. Here we provide evidence that CD40L+IL-4, IL-8 or IL-6 enhance adhesion to stromal cells, with IL-6 showing a selective effect on ZAP-70 positive cells. Stimulatory effects of IL-8 or IL-6 are fully reversed by PI3K inhibition, while the effects of CD40L+IL-4 are partially reversed. While CD40L+IL-4 is the only stimulation increasing CLL cell survival for all patient groups, IL-6 protects ZAP-70 positive cells from cell death induced by PI3K inhibition. Altogether, our results indicate that targeting the PI3K pathway can reverse protective CLL-microenvironment interactions in both ZAP-70 positive and negative CLL despite their differences in cytokine responsiveness.

[174]

TÍTULO / TITLE: - Angiogenesis inhibitors in cancer therapy: mechanistic perspective on classification and treatment rationales.

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

REVISTA / JOURNAL: - Br J Pharmacol. 2013 Oct;170(4):712-729. doi: 10.1111/bph.12344.

●● Enlace al texto completo (gratis o de pago) [1111/bph.12344](https://doi.org/10.1111/bph.12344)

AUTORES / AUTHORS: - El-Kenawi AE; El-Remessy AB

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Toxicology, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

RESUMEN / SUMMARY: - Angiogenesis, a process of new blood vessel formation, is a prerequisite for tumour growth to supply the proliferating tumour with oxygen and nutrients. The angiogenic process may contribute to tumour progression, invasion and metastasis, and is generally accepted as an indicator of tumour prognosis. Therefore, targeting tumour angiogenesis has become of high clinical relevance. The current review aimed to highlight mechanistic details of anti-angiogenic therapies and how they relate to classification and treatment rationales. Angiogenesis inhibitors are classified into either direct inhibitors that target endothelial cells in the growing vasculature or indirect inhibitors that prevent the expression or block the activity of

angiogenesis inducers. The latter class extends to include targeted therapy against oncogenes, conventional chemotherapeutic agents and drugs targeting other cells of the tumour micro-environment. Angiogenesis inhibitors may be used as either monotherapy or in combination with other anticancer drugs. In this context, many preclinical and clinical studies revealed higher therapeutic effectiveness of the combined treatments compared with individual treatments. The proper understanding of synergistic treatment modalities of angiogenesis inhibitors as well as their wide range of cellular targets could provide effective tools for future therapies of many types of cancer.

[175]

TÍTULO / TITLE: - Gene expression profiling for analysis acquired oxaliplatin resistant factors in human gastric carcinoma TSGH-S3 cells: The role of IL-6 signaling and Nrf2/AKR1C axis identification.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Oct 1;86(7):872-87. doi: 10.1016/j.bcp.2013.07.025. Epub 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.07.025](#)

AUTORES / AUTHORS: - Chen CC; Chu CB; Liu KJ; Huang CY; Chang JY; Pan WY; Chen HH; Cheng YH; Lee KD; Chen MF; Kuo CC; Chen LT

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Chang Gung Memorial Hospital at Chiayi, Chiayi, Taiwan, ROC; Chang Gung University, College of Medicine, Chang Gung Institute of Technology, Chiayi, Taiwan, ROC; Graduate Institute of Clinical Medical Sciences, Chang Gung University, Tao-Yuan, Taiwan, ROC.

RESUMEN / SUMMARY: - Oxaliplatin treatment is a mainstay of treatment for advanced gastrointestinal tract cancer, but the underlying mechanisms of acquired oxaliplatin resistance remain largely obscured. We previously demonstrated that increased DNA repair capacity and copper-transporting ATPase 1 (ATP7A) level contributed to oxaliplatin resistance in the human gastric carcinoma cell line TSGH-S3 (S3). In the present study, we applied gene array technology to identify additional resistance factors in S3 cells. We found that interleukin-6 (IL-6), aldo-keto reductase 1C1 (AKR1C1), and AKR1C3 are the top 3 upregulated genes in S3 cells when compared with parent TSGH cells. Despite a higher level of endogenous IL-6 in S3, IL-6 receptor (IR-6R, gp-80, and gp-130) levels were similar between TSGH and S3 cells. The addition of exogenous IL-6, IL-6 targeted siRNA, or neutralizing antibodies neither affected Stat3 activation, a downstream target of IL-6, nor changed oxaliplatin sensitivity in S3 cells. However, manipulation of AKR1C activity with siRNA or AKR1C inhibitors significantly reversed oxaliplatin resistance. AKR1Cs are classical antioxidant response element (ARE) genes that can be transcriptionally upregulated by nuclear factor erythroid 2-related factor 2 (Nrf2). Knockdown of Nrf2 not only decreased the levels of

AKR1C1, AKR1C2, and AKR1C3 mRNA and protein but also reversed oxaliplatin resistance in S3 cells. Taken together, these results suggest that activation of the Nrf2/AKR1C axis may contribute to oxaliplatin resistance in S3 cells but that the IL-6 signaling pathway did not contribute to resistance. Manipulation of Nrf2/AKR1Cs activity may be useful for management of oxaliplatin-refractory gastric cancers.

[176]

TÍTULO / TITLE: - Cetuximab response of lung cancer-derived EGF receptor mutants is associated with asymmetric dimerization.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-13-1145](https://doi.org/10.1158/0008-5472.CAN-13-1145)

AUTORES / AUTHORS: - Cho J; Chen L; Sangji N; Okabe T; Yonesaka K; Francis JM; Flavin RJ; Johnson W; Kwon J; Yu S; Greulich HE; Johnson BE; Eck MJ; Janne PA; Wong KK; Meyerson M

INSTITUCIÓN / INSTITUTION: - Samsung Genome Institute, Samsung Medical Center.

RESUMEN / SUMMARY: - Kinase domain mutations of the epidermal growth factor receptor (EGFR) are common oncogenic events in lung adenocarcinoma. Here we explore the dependency upon asymmetric dimerization of the kinase domain for activation of lung cancer-derived EGFR mutants. We show that while wild-type EGFR and the L858R mutant require dimerization for activation and oncogenic transformation, the exon 19 deletion, exon 20 insertion, and L858R/T790M EGFR mutants do not require dimerization. In addition, treatment with the monoclonal antibody, cetuximab, shrinks mouse lung tumors induced by the dimerization-dependent L858R mutant, but exerts only a modest effect on tumors driven by dimerization-independent EGFR mutants. These data imply that different EGFR mutants show differential requirements for dimerization, and that disruption of dimerization may be among the antitumor mechanisms of cetuximab.

[177]

TÍTULO / TITLE: - Phase I study evaluating the combination of lapatinib (a Her2/Neu and EGFR inhibitor) and everolimus (an mTOR inhibitor) in patients with advanced cancers: South West Oncology Group (SWOG) Study S0528.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep 22.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2297-4](https://doi.org/10.1007/s00280-013-2297-4)

AUTORES / AUTHORS: - Gadgeel SM; Lew DL; Synold TW; Lorusso P; Chung V; Christensen SD; Smith DC; Kingsbury L; Hoering A; Kurzrock R

INSTITUCIÓN / INSTITUTION: - Karmanos Cancer Institute, Wayne State University, 4100 John R, 4 HWCRC, Detroit, MI, 48201, USA, gadgeels@karmanos.org.

RESUMEN / SUMMARY: - PURPOSE: Everolimus, an oral inhibitor of mammalian target of rapamycin, can augment the efficacy of HER inhibitors in preclinical studies. This study was conducted to determine the safety and pharmacokinetics (PK) of the combination of lapatinib, a Her1 and 2 inhibitor, and everolimus and to describe its anti-tumor activity in the Phase I setting. METHODS: In Part I, dose escalation to define the maximum tolerated dose (MTD) was performed. In Part II, PK of both drugs were analyzed to assess drug-drug interaction. RESULTS: Twenty-three evaluable patients with advanced cancers were treated on six different dose levels in Part I of the study. The dose-limiting toxicities were diarrhea, rash, mucositis, and fatigue. The MTD of the combination was 1,250 mg of lapatinib and 5 mg of everolimus once daily. In Part II of the study, 54 patients were treated with the combination at the MTD. The mean everolimus time to maximum concentration was increased by 44 %, and mean clearance was decreased by 25 % when co-administered with lapatinib, though these differences were not statistically significant. There was no significant influence on the PK of lapatinib by everolimus. Two patients achieved a partial response [thymic cancer (45+ months) and breast cancer (unconfirmed PR; 7 months)]; 11 patients attained stable disease of at least 4 months. CONCLUSIONS: Lapatinib and everolimus are well tolerated at doses of 1,250 and 5 mg po daily, respectively. Stable disease \geq 4 months/PR was achieved in 13 of 78 patients (17 %).

[178]

TÍTULO / TITLE: - Novel mutations and expression alterations in SMAD3/TGFBR2 genes in oral carcinoma correlate with poor prognosis.

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

REVISTA / JOURNAL: - Genes Chromosomes Cancer. 2013 Nov;52(11):1042-52. doi: 10.1002/gcc.22099. Epub 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) 1002/gcc.22099

AUTORES / AUTHORS: - Sivadas VP; George NA; Kattoor J; Kannan S

INSTITUCIÓN / INSTITUTION: - Laboratory of Cell Cycle Regulation & Molecular Oncology, Division of Cancer Research, Regional Cancer Centre, Thiruvananthapuram, 695 011, Kerala, India.

RESUMEN / SUMMARY: - Transforming growth factor beta (TGF-beta) signaling is a pleiotropic cytokine signaling pathway, which controls cellular activities ranging from embryogenesis to apoptosis. Although many molecular alterations in this pathway have been described in cancers, the central point of concern, that is how these alterations influence the treatment outcome, has been addressed to a lesser extent. In this study, we have characterized the alterations of TGF-beta-SMAD signaling in 97 oral squamous cell carcinoma (OSCC) samples and assessed the association between these

alterations and the outcome of the treatment. Genomic level alteration analysis using reverse transcriptase polymerase chain reaction-single-strand conformation polymorphism/sequencing revealed that there were 25% samples harboring genomic level alterations in this pathway. Altogether, 21% samples showed TGFBR2 mutations, whereas three cases were found to harbor novel SMAD3 mutations. Notably, 14 out of 24 TGFBR2 mutations are of one type (c.*6C>A), which supplemented complementarity for hsa-miR-3189-5p. These samples showed significantly low TGFBR2 transcript levels (P = 0.026). In addition, transcript level studies using quantitative real-time PCR revealed a strong association between low TGFBR2 transcript levels and poor disease-free survival (P = 0.028) as well as poor overall survival (P = 0.013). In brief, our results showed that oral cancers with TGFBR2 downregulation comprise a different group with more aggressive nature. These results suggest that in OSCCs, TGFBR2 transcript levels may be developed as a promising prognostic biomarker. Furthermore, for the first time, this study reports SMAD3 mutations in oral carcinoma. © 2013 Wiley Periodicals, Inc.

[179]

TÍTULO / TITLE: - Neuroblastoma of undifferentiated subtype, prognostic significance of prominent nucleolar formation, and MYC/MYCN protein expression: A report from the Children's Oncology Group.

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

REVISTA / JOURNAL: - Cancer. 2013 Jul 30. doi: 10.1002/cncr.28251.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28251](#)

AUTORES / AUTHORS: - Wang LL; Sukanuma R; Ikegaki N; Tang X; Naranjo A; McGrady P; London WB; Hogarty MD; Gastier-Foster JM; Look AT; Park JR; Maris JM; Cohn SL; Seeger RC; Shimada H

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles and University of Southern California Keck School of Medicine, Los Angeles, California.

RESUMEN / SUMMARY: - BACKGROUND: This study sought to investigate biological/clinicopathological characteristics of neuroblastoma, undifferentiated subtype (NBUD). METHODS: This study examined 157 NBUD cases filed at the Children's Oncology Group Neuroblastoma Pathology Reference Laboratory, and survival rates of the patients were analyzed with known prognostic factors. Immunostainings for MYCN and MYC protein were performed on 68 tumors. RESULTS: NBUD cases had a poor prognosis (48.4% +/- 5.0% 3-year event-free survival [EFS]; 56.5% +/- 5.0% overall survival [OS]), and were often associated with high mitosis-karyorrhexis index (MKI, 65%), prominent nucleoli (PN, 83%), >= 18 months of age (75%), MYCN amplification (MYCN-A, 83%), diploid pattern (63%), and 1pLOH (loss of heterozygosity (72%). However, these prognostic indicators, except for MYCN status,

had no significant impact on survival. Surprisingly, EFS for patients with MYCN-A tumors (53.4% +/- 5.6%) was significantly better (P = .0248) than for patients with MYCN-nonamplified (MYCN-NA) tumors (31.7% +/- 11.7%), with MYCN-NA and PN (+) tumors having the worst prognosis (9.3% +/- 8.8%, P = .0045). Immunohistochemically, MYCN expression was found in 42 of 48 MYCN-A tumors. In contrast, MYC expression was almost exclusively found in the MYCN-NA tumors (9 of 20) especially when they had PN (8 of 11). Those patients with only MYC-positive tumors had the worst EFS (N = 8, 12.5% +/- 11.7%) compared with only MYCN-positive (N = 39, 49.9% +/- 17.7%) and both negative tumors (N = 15, 70.0% +/- 17.1%) (P = .0029). High MKI was often found in only MYCN-positive (30 of 38) but rarely in only MYC-positive (2 of 8) tumors. CONCLUSIONS: NBUD represents a unique subtype of neuroblastoma associated with a poor prognosis. In this subtype, MYC protein expression may be a new prognostic factor indicating more aggressive clinical behavior than MYCN amplification and subsequent MYCN protein expression. Cancer 2013. © 2013 American Cancer Society.

[180]

TÍTULO / TITLE: - Evaluating gene expression profiling by quantitative polymerase chain reaction to develop a clinically feasible test for outcome prediction in multiple myeloma.

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

REVISTA / JOURNAL: - Br J Haematol. 2013 Aug 16. doi: 10.1111/bjh.12519.

●● [Enlace al texto completo \(gratis o de pago\) 1111/bjh.12519](#)

AUTORES / AUTHORS: - Sarasquete ME; Martinez-Lopez J; Chillon MC; Alcoceba M; Corchete LA; Paiva B; Puig N; Sebastian E; Jimenez C; Mateos MV; Rosinol L; Palomera L; Teruel AI; Gonzalez Y; Lahuerta JJ; Blade J; Gutierrez NC; Fernandez-Redondo E; Gonzalez M; San Miguel JF; Garcia-Sanz R

INSTITUCIÓN / INSTITUTION: - Servicio de Hematología, Hospital Universitario de Salamanca e Instituto Biosanitario de Salamanca (IBSAL), Universidad de Salamanca, Salamanca, España; Centro de Investigación del Cáncer de Salamanca, Salamanca, España.

RESUMEN / SUMMARY: - The gene expression profiles (GEPs) of 96 selected genes were analysed by real-time quantitative polymerase chain reaction (qPCR) with a TaqMan low-density array card in isolated tumour plasma cells (PCs) from 157 newly diagnosed multiple myeloma (MM) patients. This qPCR-based GEP correctly classified cases following the Translocation-cyclin D classification. Classic prognostic parameters and qPCR-based GEP predicted MM patient outcome and, although multivariate analyses revealed that cytogenetic risk (standard vs. high risk) was the variable that most strongly predicted prognosis, GEP added significant information for risk stratification. Considering only the standard risk cytogenetic patients, multivariate analyses revealed that high beta2-microglobulin, low CDKN1A and high SLC19A1 gene expression levels

independently predicted a short time-to-progression (TTP), while high International Staging System stage, low CDKN2B and high TBRG4 gene expression predicted poor overall survival (OS). A gene expression risk score enabled the division of standard risk patients into two groups with different TTPs (83% vs. 38% at 3 years, $P < 0.0001$) and OS rates (88% vs. 61% at 5 years; $P = 0.003$). This study demonstrates that quantitative PCR is a robust, accurate and feasible technique for implementing in the daily routine as a surrogate for GEP-arrays.

[181]

TÍTULO / TITLE: - Glucose-regulated protein 94 modulates the therapeutic efficacy to taxane in cervical cancer cells.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 9.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1056-9](#)

AUTORES / AUTHORS: - Tai CJ; Wang JW; Su HY; Tai CJ; Wang CK; Wu CT; Lien YC; Chang YJ

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan.

RESUMEN / SUMMARY: - Cervical cancer is an important health issue for women worldwide, and the endoplasmic reticulum stress pathway is important for determining the chemotherapeutic response to cancer. However, the role of glucose-regulated protein 94 (GRP94) in taxane therapy for cervical cancer remains unclear. In this study, we generated GRP94 knockdown (GRP94-KD) HeLa cells using short hairpin RNAs and found that GRP94-KD cells were resistant to taxane treatment in an MTT assay. Scrambled control cells demonstrated higher levels of apoptosis when treated with taxanes in comparison to GRP94-KD cells, as determined by cell cycle profiling, 4',6-diamidino-2-phenylindole staining, and terminal deoxynucleotidyl transferase-mediated nick end labeling staining. Caspase 3 and caspase 7 activity was also higher in scrambled control cells treated with taxane in comparison to GRP94-KD cells. Moreover, we found that depletion of GRP94 altered the levels of the apoptosis-related proteins Bcl2 and Bad, leading to sensitivity to taxane. Exposure to taxane also induced the expression of Bad in scrambled cells but not in GRP94-KD cells. In addition, the expression of Bcl2 was increased dramatically in GRP94-KD cells, whereas only a small increase was observed in scrambled cells. Therefore, we conclude that silencing GRP94 may increase resistance to taxane treatment in cervical cancer cells by altering the activation of the apoptosis pathway. In addition, GRP94 may represent a key biomarker for determining the therapeutic efficacy of taxane treatment in cervical cancer patients.

[182]

TÍTULO / TITLE: - Deletion of Irf5 protects hematopoietic stem cells from DNA damage-induced apoptosis and suppresses gamma-irradiation-induced thymic lymphomagenesis.

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

REVISTA / JOURNAL: - Oncogene. 2013 Aug 5. doi: 10.1038/onc.2013.295.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.295](#)

AUTORES / AUTHORS: - Bi X; Feng D; Korczeniewska J; Alper N; Hu G; Barnes BJ

INSTITUCIÓN / INSTITUTION: - 1] Department of Biochemistry and Molecular Biology, New Jersey Medical School, UMDNJ, Newark, NJ, USA [2] New Jersey Medical School-University Hospital Cancer Center, UMDNJ, Newark, NJ, USA.

RESUMEN / SUMMARY: - Repeated low-dose gamma-irradiation (IR) induces thymic lymphoma in mice because of oncogenic mutations propagating from a primitive hematopoietic stem/progenitor cell (HSC) in the bone marrow. It is well known that IR-induced thymic lymphomagenesis is markedly enhanced by p53 deficiency, yet data also indicate that p53-dependent apoptosis can actively drive tumor formation in this model. The latter was recently expounded on by findings from Puma-deficient mice, indicating that loss of this proapoptotic p53 target gene results in protection from IR-induced lymphomagenesis rather than enhanced susceptibility to. Similar to Puma, the transcription factor interferon regulatory factor 5 (Irf5) has been reported as a p53 target gene and is required for DNA damage-induced apoptosis. To date, no studies have been performed to elucidate the in vivo role of IRF5 in tumorigenesis. Given its essential role in DNA damage-induced apoptosis, we explored the tumor suppressor function of IRF5 in IR-induced thymic lymphomagenesis. Somewhat surprisingly, we found that thymic lymphoma development was significantly suppressed in Irf5^{-/-} mice as compared with wild-type littermates. Suppression was due, in part, to reduced thymocyte and HSC apoptosis, resulting in reduced compensatory proliferation, and reduced replication stress-associated DNA damage. The observed effects were independent of p53 or Puma as these proteins were upregulated in Irf5^{-/-} mice in response to IR. This study demonstrates an important new role for IRF5 in maintaining HSC homeostasis after IR and supports the non-redundant functions of IRF5, p53 and PUMA in DNA damage-induced lymphomagenesis. We propose that IRF5 may be an attractive target for developing therapeutic agents to ameliorate radiation-induced bone marrow injury. Oncogene advance online publication, 5 August 2013; doi:10.1038/onc.2013.295.

[183]

TÍTULO / TITLE: - Predictive value of ERCC1, ERCC2, and XRCC1 overexpression for stage III colorectal cancer patients receiving FOLFOX-4 adjuvant chemotherapy.

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

REVISTA / JOURNAL: - J Surg Oncol. 2013 Aug 31. doi: 10.1002/jso.23422.

●● Enlace al texto completo (gratis o de pago) [1002/jso.23422](https://doi.org/10.1002/jso.23422)

AUTORES / AUTHORS: - Huang MY; Tsai HL; Lin CH; Huang CW; Ma CJ; Huang CM; Chai CY; Wang JY

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; Department of Radiation Oncology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - **OBJECTIVES:** To determine the correlation between expression of three DNA repair genes and early failure/clinical outcome of stage III colorectal cancer (CRC) patients administered with FOLFOX-4, including the excision repair cross-complementation group 1 (ERCC1), the excision repair cross-complementing 2 (ERCC2), and X-ray repair cross-complementing protein 1 (XRCC1). **MATERIALS AND METHODS:** We retrospectively analyzed clinicopathological features and ERCC1, ERCC2, XRCC1 expressions by immunohistochemical staining in 180 stage III CRC patients undergoing curative resection and treated with FOLFOX-4 chemotherapy to identify predictors of postoperative early failure. **RESULTS:** Among 180 CRC patients, 44 patients were classified into early failure group, and 136 patients were categorized into non-early failure group. A multivariate logistic regression analysis showed that ERCC1 overexpression ($P = 0.005$), and high postoperative carcinoembryonic antigen (CEA) levels ($P = 0.001$) were independent predictors of early failure. Additionally, ERCC1 overexpression was not only a predictor of early failure but also for disease-free survival ($P < 0.001$) and overall survival ($P < 0.001$). However, no predictive roles of ERCC2 and XRCC1 expression among these analyzed patients. **CONCLUSIONS:** ERCC1 overexpression is an important predictor of early failure in patients with stage III CRC administering FOLFOX-4 adjuvant chemotherapy and this marker may help identify patients who would benefit from intensive follow-up and enhance therapeutic programs. J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

[184]

TÍTULO / TITLE: - High-dose melphalan produces favorable response in a patient with multiple myeloma and coexisting essential thrombocythemia with JAK2 mutation.

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

REVISTA / JOURNAL: - Bone Marrow Transplant. 2013 Aug 12. doi: 10.1038/bmt.2013.117.

●● Enlace al texto completo (gratis o de pago) [1038/bmt.2013.117](https://doi.org/10.1038/bmt.2013.117)

AUTORES / AUTHORS: - Nishihori T; Hassoun Y; Shain K; Alsina M; Kharfan-Dabaja MA

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Oncological Sciences, H. Lee Moffitt Cancer Center/University of South Florida College of Medicine, Tampa, FL, USA.

[185]

TÍTULO / TITLE: - Synergistic anti breast cancer effect of a combined treatment with the methyl donor S-adenosyl methionine (SAM) with the DNA methylation inhibitor 5-aza-2'-deoxycytidine.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt284](#)

AUTORES / AUTHORS: - Chik F; Machnes Z; Szyf M

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Therapeutics, McGill University, 3655 Promenade Sir William Osler, Montreal, Quebec, H3G 1Y6, Canada.

RESUMEN / SUMMARY: - DNA demethylating agents activate tumor suppressor genes that are silenced by DNA methylation in cancer and are therefore emerging as a novel approach to cancer therapy. 5-azacytidine (VIDAZA), the first representative of this class of drugs was approved for treatment of myelodysplastic syndromes and is currently being tested on other cancers including solid tumors. However, 5-azacytidine or its deoxy-analogue (5-azaCdR) could also induce methylated pro-metastatic genes by DNA demethylation and induce cancer cell invasiveness. Since 5-azacytidine is a potent cancer growth inhibitor, we tested whether combining it with a DNA methylating agent, the methyl donor S-adenosylmethionine (SAM), would block the adverse demethylating activity of 5-azaCdR while maintaining its growth suppression effects. We show here using several invasive and non-invasive breast cancer cell lines that SAM inhibits global and gene specific demethylation induced by 5-azaCdR, prevents 5-azaCdR activation of pro-metastatic genes uPA and MMP2, resulting in inhibition of cell invasiveness while augmenting the growth inhibitory effects of 5-azaCdR and its effects on tumor suppressor genes. Combination of drugs acting on the DNA methylation machinery at different levels is proposed as a new strategy for epigenetic therapy of cancer.

[186]

TÍTULO / TITLE: - Pharmacogenetic determinants associated with sunitinib-induced toxicity and ethnic difference in Korean metastatic renal cell carcinoma patients.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Oct;72(4):825-35. doi: 10.1007/s00280-013-2258-y. Epub 2013 Sep 8.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2258-y](#)

AUTORES / AUTHORS: - Kim HR; Park HS; Kwon WS; Lee JH; Tanigawara Y; Lim SM; Kim HS; Shin SJ; Ahn JB; Rha SY

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Korea.

RESUMEN / SUMMARY: - PURPOSE: The aim of this study was to investigate the pharmacogenetic determinants of sunitinib-related toxicity and ethnic difference in metastatic renal cell carcinoma (mRCC) among Korean patients. METHODS: A pharmacogenetic study was performed in 65 patients with mRCC treated with the standard schedule of sunitinib (50 mg orally once daily for 4 weeks-on/2 weeks-off). Detailed data regarding the toxicity of sunitinib, including thrombocytopenia, neutropenia, anemia, and hand-foot syndrome (HFS), were prospectively collected in a clinical trial program (n = 38) or standard oncology practice (n = 27). Total of 12 genetic polymorphisms in 8 candidate genes (CYP1A1, CYP3A5, ABCB1, ABCG2, PDGFRalpha, VEGFR2, RET, and FLT3) were analyzed for an association with treatment-related toxicity from sunitinib using Pearson chi (2) test. RESULTS: Common grade 3 or grade 4 treatment-related toxicities were thrombocytopenia (36.9 %, 24/65), neutropenia (18.4 %, 12/65), anemia (7.7 %, 5/65), and HFS (12.3 %, 8/65). Patients carrying an ABCG2 421 AA genotype developed significantly more grade 3 or grade 4 thrombocytopenia, neutropenia, and HFS adjusted for age, sex, and Eastern Cooperative Oncology Group performance status, and body surface area (odds ratio compared with AC/CC genotypes [OR] 9.90, P = 0.04, thrombocytopenia; OR 18.20, P = 0.02, neutropenia; and OR 28.46, P = 0.01, HFS). In addition, total and surface protein ABCG2 protein expression was decreased in ABCG2 421 AA mutant cells compared to wild type. CONCLUSION: Among 12 genetic polymorphisms, polymorphism in the ABCG2 421C>A gene may be mostly associated with the risk of sunitinib-related toxicity in mRCC patients. Considering the high frequency of 421C>A SNP in Asian, this may be related to differential toxicities among ethnic groups.

[187]

TÍTULO / TITLE: - Low expression of long noncoding RNA GAS6-AS1 predicts a poor prognosis in patients with NSCLC.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):694. doi: 10.1007/s12032-013-0694-5. Epub 2013 Aug 24.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12032-013-0694-5](#)

AUTORES / AUTHORS: - Han L; Kong R; Yin DD; Zhang EB; Xu TP; De W; Shu YQ

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Xuzhou Central Hospital, Affiliated Xuzhou Hospital, College of Medicine, Southeast University, Xuzhou, 221000, Jiangsu, China, hanliang801223@foxmail.com.

RESUMEN / SUMMARY: - Lung cancer is the most frequent cancer in China and all over the world. Recent studies have shown that long noncoding RNAs play critical roles in multiple biological processes including oncogenesis. In this study, we reported a new lncRNA GAS6-AS1 (GAS6 antisense RNA 1), whose expression was downregulated in tumor tissues in 50 patients with non-small cell lung cancer (NSCLC) compared with those in the adjacent normal tissues ($P < 0.001$). Furthermore, decreased GAS6-AS1 expression was negatively correlated with lymph node metastasis ($P = 0.032$) and advanced tumor node metastasis stage ($P = 0.003$). Univariate and multivariate analyses showed that GAS6-AS1 expression served as an independent predictor for overall survival ($P = 0.036$). Also, GAS6-AS1 level was inversely correlated with GAS6 (growth-arrest-specific gene6) mRNA level (Pearson's correlation -0.620). In conclusion, our study demonstrated that altered lncRNA GAS6-AS1 expression might be involved in the development and progression of NSCLC by influencing its host gene and promised to be a potential diagnostic target in patients with NSCLC.

[188]

TÍTULO / TITLE: - Receptor-like protein tyrosine phosphatase kappa negatively regulates the apoptosis of prostate cancer cells via the JNK pathway.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1560-8. doi: 10.3892/ijo.2013.2082. Epub 2013 Aug 29.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2082](#)

AUTORES / AUTHORS: - Sun PH; Ye L; Mason MD; Jiang WG

INSTITUCIÓN / INSTITUTION: - Metastasis and Angiogenesis Research Group, Institute of Cancer and Genetics, Cardiff University School of Medicine, Cardiff CF14 4XN, UK.

RESUMEN / SUMMARY: - Receptor-like protein tyrosine phosphatase kappa (PTPRK) has been indicated as a putative tumour suppressor in primary central nervous system lymphomas and colorectal cancer. The present study investigated the expression of PTPRK in prostate cancer and the biological impact of PTPRK on prostate cancer cells. The expression of the PTPRK protein and transcript in prostate cancer was examined using IHC and PCR. Knockdown of PTPRK in prostate cancer cells was performed using a specific anti-PTPRK transgene. The impact of PTPRK knockdown on prostate cancer cells was evaluated using in vitro cell models and the apoptosis was analysed using flow cytometry. PTPRK expression was increased in prostate cancer tissues and knockdown of PTPRK in PC-3 cells suppressed the in vitro cell growth in which an increased apoptotic population was seen. Accompanied with the knockdown of PTPRK, increased expression of caspase-3, caspase-8 and p53, and a decreased ID1 expression were evident in the cells. Furthermore, an increased tyrosine phosphorylated c-Jun N-terminal kinase (JNK) was seen in the PTPRK knockdown cells. The effect on apoptosis was diminished by a JNK inhibitor. In conclusion, PTPRK knockdown resulted in

increased apoptosis leading to the inhibition of in vitro growth of prostate cancer cells. PTPRK is a key factor in coordinating apoptosis via the regulation of MAPK pathways, in particular the JNK pathway in prostate cancer cells.

[189]

TÍTULO / TITLE: - Prognostic Factors of Metastatic or Recurrent Esophageal Squamous Cell Carcinoma in Patients Receiving Three-drug Combination Chemotherapy.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):4123-8.

AUTORES / AUTHORS: - Chen WW; Lin CC; Huang TC; Cheng AL; Yeh KH; Hsu CH

INSTITUCIÓN / INSTITUTION: - Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10002, Taiwan, R.O.C.

chihhungshu@ntu.edu.tw.

RESUMEN / SUMMARY: - BACKGROUND: Three-drug combination therapy based on cisplatin/fluorouracil might improve treatment efficacy for metastatic esophageal squamous cell carcinoma (ESCC), but at the risk of increasing toxicity. The study sought to identify factors associated with outcomes of metastatic ESCC in patients who were treated with three-drug combinations. PATIENTS AND METHODS: One-hundred and thirteen patients with metastatic or recurrent ESCC who were treated with cisplatin/fluorouracil-based three-drug combination during 2000-2009 were studied. The prognostic impact of clinicopathological characteristics were evaluated by Cox proportional hazard regression analyses. RESULTS: The third chemotherapeutic agents comprised of paclitaxel, docetaxel, and methotrexate in 76 (67%), 13 (12%), and 24 (21%) of patients, respectively. The overall response rate was 41%. The median overall survival (OS) was 8.5 months. Results of the Cox proportional hazard regression models showed that age ≥ 65 years, Eastern Cooperative Oncology Group performance status of 0 and 1, lymph node-only metastasis and baseline white blood cell (WBC) count $\leq 10,000/\text{mm}^3$ were significant prognostic factors for better OS. The OS curves were significantly separated by risk groups comprising of age, metastasis status and WBC count as risk factors. CONCLUSION: The identification of prognostic factors could facilitate for future design of randomized studies on the efficacy of three-drug combinations for metastatic ESCC.

[190]

TÍTULO / TITLE: - Early detection of neutralizing antibodies to interferon-beta in multiple sclerosis patients: binding antibodies predict neutralizing antibody development.

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

REVISTA / JOURNAL: - Mult Scler. 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1177/1352458513503597](https://doi.org/10.1177/1352458513503597)

AUTORES / AUTHORS: - Hegen H; Millonig A; Bertolotto A; Comabella M; Giovanonni G; Guger M; Hoelzl M; Khalil M; Killestein J; Lindberg R; Malucchi S; Mehling M; Montalban X; Polman C; Rudzki D; Schautzer F; Sellebjerg F; Sorensen P; Deisenhammer F

INSTITUCIÓN / INSTITUTION: - Department of Neurology, Innsbruck Medical University, Austria.

RESUMEN / SUMMARY: - BACKGROUND: Neutralizing antibodies (NAb) affect efficacy of interferon-beta (IFN-b) treatment in multiple sclerosis (MS) patients. NABs evolve in up to 44% of treated patients, usually between 6-18 months on therapy. OBJECTIVES: To investigate whether early binding antibody (BAb) titers or different IFN-b biomarkers predict NAb evolution. METHODS: We included patients with MS or clinically isolated syndrome (CIS) receiving de novo IFN-b treatment in this prospective European multicenter study. Blood samples were collected at baseline, before and after the first IFN-b administration, and again after 3, 12 and 24 months on that therapy; for determination of NABs, BAb, gene expression of MxA and protein concentrations of MMP-9, TIMP-1, sTRAIL, CXCL-10 and CCL-2. RESULTS: We found that 22 of 164 (13.4%) patients developed NABs during a median time of 23.8 months on IFN-b treatment. Of these patients, 78.9% were BAb-positive after 3 months. BAb titers \geq 1:2400 predicted NAb evolution with a sensitivity of 74.7% and a specificity of 98.5%. Cross-sectionally, MxA levels were significantly diminished in the BAb/NAb-positive samples; similarly, CXCL-10 and sTRAIL concentrations in BAb/NAb-positive and BAb-positive/NAb-negative samples, respectively, were also diminished compared to BAb/NAb-negative samples. CONCLUSIONS: BAb titers reliably predict NABs. CXCL-10 is a promising sensitive biomarker for IFN-b response and its abrogation by anti-IFN-b antibodies.

[191]

TÍTULO / TITLE: - CTNNB1 45F mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence: An independent, multicenter validation study.

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

REVISTA / JOURNAL: - Cancer. 2013 Jul 31. doi: 10.1002/cncr.28271.

●● Enlace al texto completo (gratuito o de pago) [1002/cncr.28271](#)

AUTORES / AUTHORS: - Colombo C; Miceli R; Lazar AJ; Perrone F; Pollock RE; Le Cesne A; Hartgrink HH; Cleton-Jansen AM; Domont J; Bovee JV; Bonvalot S; Lev D; Gronchi A

INSTITUCIÓN / INSTITUTION: - Sarcoma Service, Department of Surgery, Scientific Institute for Research, Hospitalization, and Health Care (IRCCS) Foundation, National Cancer Institute, Milan, Italy.

RESUMEN / SUMMARY: - BACKGROUND: A role for the serine to phenylalanine substitution at codon 45 (the S45F mutation) in the catenin (cadherin-associated

protein) beta-1 (CTNNB1) gene as a molecular predictor of local recurrence in patients with primary, sporadic desmoid tumor (DT) has been reported. To confirm the previous data, the authors evaluated the correlation between CTNNB1 mutation type and local recurrence in this multi-institutional, retrospective study. METHODS: Patients with primary, sporadic DT who underwent macroscopic complete surgical resection were included. Recurrence-free survival (RFS) analyses were conducted using the Kaplan-Meier method and log-rank tests to compare strata. RESULTS: In total, 179 patients were identified, including 65% females and 35% males (median age, 39 years; median tumor size, 7 cm). Most DTs were located in the abdominal/chest wall (42%) followed by extra-abdominal sites (40%) and intra-abdominal sites (18%). All patients underwent either R0 resection (62%) or R1 resection (38%), and most underwent surgery alone (80%). The tyrosine to alanine substitution at codon 41 (T41A) was the most frequent mutation (45%), but the S45F mutation was more prevalent in extra-abdominal DTs compared with other sites ($P < .001$). At a median follow-up of 50 months, 86% of patients remained alive without disease. The estimated 3-year and 5-year RFS rates were 0.49 and 0.45, respectively, for patients who had tumors with the S45F mutation; 0.91 and 0.91, respectively, for patients who had wild-type tumors; and 0.70 and 0.66, respectively, for all others ($P < .001$). A similar trend was observed for patients who underwent surgery alone ($P < .001$). On multivariable analysis, mutation remained the only factor that was prognostic for local recurrence. CONCLUSIONS: This series confirmed that primary, completely resected, sporadic DTs with the S45F mutation have a greater tendency for local recurrence. With increasing implementation of “watchful-waiting” for DT management, it will be important to determine whether mutation type predicts outcome for these patients. Cancer 2013. © 2013 American Cancer Society.

[192]

TÍTULO / TITLE: - Inhibition of the mitochondrial pyrimidine biosynthesis enzyme dihydroorotate dehydrogenase by doxorubicin and brequinar sensitizes cancer cells to TRAIL-induced apoptosis.

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

REVISTA / JOURNAL: - Oncogene. 2013 Sep 9. doi: 10.1038/onc.2013.313.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.313](#)

AUTORES / AUTHORS: - He T; Haapa-Paananen S; Kaminsky VO; Kohonen P; Fey V; Zhivotovsky B; Kallioniemi O; Perala M

INSTITUCIÓN / INSTITUTION: - Medical Biotechnology, VTT Technical Research Centre of Finland, Turku, Finland.

RESUMEN / SUMMARY: - Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising agent in selectively killing tumor cells. However, TRAIL monotherapy has not been successful as many cancer cells are resistant to TRAIL. Chemotherapeutic

agents, such as doxorubicin have been shown to act synergistically with TRAIL, but the exact mechanisms of actions are poorly understood. In this study, we performed high-throughput small interfering RNA screening and genome-wide gene expression profiling on doxorubicin-treated U1690 cells to explore novel mechanisms underlying doxorubicin-TRAIL synergy. The screening and expression profiling results were integrated and dihydroorotate dehydrogenase (DHODH) was identified as a potential candidate. DHODH is the rate-limiting enzyme in the pyrimidine synthesis pathway, and its expression was downregulated by doxorubicin. We demonstrated that silencing of DHODH or inhibition of DHODH activity by brequinar dramatically increased the sensitivity of U1690 cells to TRAIL-induced apoptosis both in 2D and 3D cultures, and was accompanied by downregulation of c-FLIPL as well as by mitochondrial depolarization. In addition, uridine, an end product of the pyrimidine synthesis pathway was able to rescue the sensitization effects initiated by both brequinar and doxorubicin. Furthermore, several other cancer cell lines, LNCaP, MCF-7 and HT-29 were also shown to be sensitized to TRAIL by brequinar. Taken together, our findings have identified a novel protein target and its inhibitor, brequinar, as a potential agent in TRAIL-based combinatorial cancer therapy and highlighted for the first time the importance of mitochondrial DHODH enzyme and pyrimidine pathway in mediating TRAIL sensitization in cancer cells. Oncogene advance online publication, 9 September 2013; doi:10.1038/onc.2013.313.

[193]

TÍTULO / TITLE: - Impact of promoter polymorphisms in key regulators of the intrinsic apoptosis pathway in childhood acute lymphoblastic leukemia outcome.

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

REVISTA / JOURNAL: - Haematologica. 2013 Sep 13.

●● [Enlace al texto completo \(gratis o de pago\) 3324/haematol.2013.085340](#)

AUTORES / AUTHORS: - Sanchez R; St-Cyr J; Lalonde ME; Healy J; Richer C; Gagne V; Laverdiere C; Silverman LB; Sallan SE; Neuberg D; Kutok JL; Kritikou EA; Krajcinovic M; Sinnett D

INSTITUCIÓN / INSTITUTION: - CHU Sainte-Justine Research Center, Montreal, Canada;

RESUMEN / SUMMARY: - The introduction of multiagent treatment protocols has led to a remarkable increase in survival rates for children diagnosed with acute lymphoblastic leukemia, yet for a subpopulation of patients, resistance to chemotherapeutics remains an obstacle to successful treatment. Here we investigate the role of the mitochondrial apoptosis pathway (or intrinsic) in modulating childhood acute lymphoblastic leukemia onset and outcomes. Cell death is a highly regulated process that plays an essential role in regulating cell homeostasis, particularly in tissues with high intrinsic proliferating capacity such as the hematopoietic system. Following the underlying paradigm that cis-acting genetic variation can influence disease risk and

outcomes by modulating gene expression, we performed a systematic analysis of the proximal promoter regions of 21 genes involved in apoptosis. Using gene reporter assays, we show that promoter variation in 11 intrinsic apoptosis genes including ADPRT, APAF1, BCL2, BAD, BID, MCL1, BIRC4, BCL2L1, ENDOG, YWHAB and YWHAQ, influence promoter activity in an allele-specific manner. We also show that correlated promoter variation and increased expression of MCL1 is associated with reduced overall survival among high-risk patients receiving higher doses of corticosteroid, suggesting that increased expression of this anti-apoptosis gene could lead to reduced cell death and influence treatment response in a disease and dose-responsive manner.

[194]

TÍTULO / TITLE: - Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Oct;139(10):1691-700. doi: 10.1007/s00432-013-1495-0. Epub 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1495-0](#)

AUTORES / AUTHORS: - Yoshida T; Ishii G; Goto K; Yoh K; Niho S; Umemura S; Matsumoto S; Ohmatsu H; Nagai K; Ohe Y; Ochiai A

INSTITUCIÓN / INSTITUTION: - Division of Pathology, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan.

RESUMEN / SUMMARY: - BACKGROUND: The efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) differs in patients with lung adenocarcinoma harboring EGFR-activating mutations. Although lung adenocarcinoma with EGFR-activating mutations has heterogeneous morphologic features, the predictive role of histologic subtype of lung adenocarcinoma with regard to the effectiveness of EGFR-TKIs in patients with EGFR-activating mutations has not been well defined. METHODS: Among 134 postoperative recurrence patients with lung adenocarcinoma harboring EGFR-activating mutation (L858R or exon 19 deletion) treated with EGFR-TKIs, we retrospectively analyzed 61 patients treated with EGFR-TKIs as first-line chemotherapy. All the tumors were classified according to the new histologic classification proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) into the following subtypes: lepidic, papillary, acinar, micropapillary, or solid predominant subtype. We evaluated the correlation between the histologic subtype and the clinical efficacy of EGFR-TKIs. RESULTS: In overall response rate, adenocarcinoma with solid predominant subtype is significantly worse than with non-solid predominant subtype (61 vs. 88 %, P = 0.03). The median progression-free survival (PFS) and overall survival after EGFR-TKI treatment were significantly shorter

for the patients with solid predominant subtype than for those with non-solid predominant subtype (median PFS of 7.7 vs. 13.5 months, $P = 0.002$, and median OS of 21.5 vs. 31.0 months, $P = 0.028$). CONCLUSIONS: This study indicated that among patients with lung adenocarcinoma harboring activating EGFR mutations treated with EGFR-TKIs, solid predominant subtype according to IASLC/ATS/ERS classification is a response predictor for EGFR-TKI.

[195]

TÍTULO / TITLE: - HLA and Killer Immunoglobulin-like Receptor Genes as Outcome Predictors of Hepatitis C Virus-Related Hepatocellular Carcinoma.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5465-5473. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0986](#)

AUTORES / AUTHORS: - Cariani E; Pilli M; Zerbini A; Rota C; Olivani A; Zanelli P; Zanetti A; Trenti T; Ferrari C; Missale G

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Clinical Pathology-Toxicology, Ospedale S. Agostino-Estense, Modena; U.O. Infectious Diseases and Hepatology; U.O. Medical Genetics, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; and Clinical Immunology, Allergy and Advanced Biotechnologies Unit, Department of Laboratory Medicine, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy.

RESUMEN / SUMMARY: - PURPOSE: We evaluated the impact of the killer immunoglobulin-like receptors (KIR) of natural killer (NK) cells and of their HLA ligands over the clinical outcome of hepatitis C virus (HCV)-related hepatocellular carcinoma after curative treatment by either surgical resection or radiofrequency thermal ablation (RTA). EXPERIMENTAL DESIGN: Sixty-one consecutive patients with HCV-related hepatocellular carcinoma underwent KIR genotyping and HLA typing. A phenotypic/functional characterization of NK cells was carried out in patients with different KIR/KIR-ligand genotype. RESULTS: Activating KIR2DS5 was associated with significantly longer time to recurrence (TTR) and overall survival (OS; $P < 0.03$ each). Homozygous HLA-C1 ($P < 0.02$) and HLA-Bw4I80 ($P < 0.05$) were expressed by patients with significantly better OS, whereas HLA-C2 ($P < 0.02$) and HLA-Bw4T80 ($P < 0.01$) were associated with a worse OS. Multivariate analysis identified as parameters independently related to TTR the type of treatment (surgical resection vs. RTA; $P < 0.03$) and HLA-C1 ($P < 0.03$), whereas only KIR2DS5 was an independent predictor of longer OS ($P < 0.05$). Compound KIR2DL2-C1 and KIR3DS1-Bw4T80 genotypes were associated with better TTR ($P < 0.03$) and worse OS ($P = 0.02$), respectively. A prevalent cytotoxic (CD56dim) NK phenotype was detected in patients with both longer TTR and OS. Cytotoxic capacity measured by upregulation of CD107a was significantly higher in subjects with HLA-C1 alone or combined with KIR2DL2/KIR2DL3. CONCLUSIONS: These

results support a central role of NK cells in the immune response against hepatocellular carcinoma, providing a strong rationale for therapeutic strategies enhancing NK response and for individualized posttreatment monitoring schemes. Clin Cancer Res; 19(19); 5465-73. ©2013 AACR.

[196]

TÍTULO / TITLE: - Depletion of hepatoma-derived growth factor-related protein-3 induces apoptotic sensitization of radioresistant A549 cells via reactive oxygen species-dependent p53 activation.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 27;439(3):333-9. doi: 10.1016/j.bbrc.2013.08.086. Epub 2013 Sep 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.08.086](https://doi.org/10.1016/j.bbrc.2013.08.086)

AUTORES / AUTHORS: - Yun HS; Hong EH; Lee SJ; Baek JH; Lee CW; Yim JH; Um HD; Hwang SG

INSTITUCIÓN / INSTITUTION: - Division of Radiation Cancer Biology, Korea Institute of Radiological & Medical Sciences, Seoul 139-706, Republic of Korea; Department of Chemistry, College of Natural Sciences, Hanyang University, Seoul 133-791, Republic of Korea.

RESUMEN / SUMMARY: - Biomarkers based on functional signaling have the potential to provide greater insight into the pathogenesis of cancer and may offer additional targets for anticancer therapeutics. Here, we identified hepatoma-derived growth factor-related protein-3 (HRP-3) as a radioresistance-related gene and characterized the molecular mechanism by which its encoded protein regulates the radio- and chemoresistant phenotype of lung cancer-derived A549 cells. Knockdown of HRP-3 promoted apoptosis of A549 cells and potentiated the apoptosis-inducing action of radio- and chemotherapy. This increase in apoptosis was associated with a substantial generation of reactive oxygen species (ROS) that was attributable to inhibition of the Nrf2/HO-1 antioxidant pathway and resulted in enhanced ROS-dependent p53 activation and p53-dependent expression of PUMA (p53 upregulated modulator of apoptosis). Therefore, the HRP-3/Nrf2/HO-1/ROS/p53/PUMA cascade is an essential feature of the A549 cell phenotype and a potential radiotherapy target, extending the range of targets in multimodal therapies against lung cancer.

[197]

TÍTULO / TITLE: - Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 12. doi: 10.1002/ijc.28436.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28436](https://doi.org/10.1002/ijc.28436)

AUTORES / AUTHORS: - Bidard FC; Madic J; Mariani P; Piperno-Neumann S; Rampanou A; Servois V; Cassoux N; Desjardins L; Milder M; Vaucher I; Pierga JY; Lebofsky R; Stern MH; Lantz O

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Institut Curie, Paris, France; Laboratory of Circulating Tumor Biomarkers, Institut Curie, Paris, France.

RESUMEN / SUMMARY: - Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) have been recently investigated in several cancer types, but their respective clinical significance remains to be determined. In our prospective study, we compared the detection rate and the prognostic value of these two circulating biomarkers in patients with metastatic uveal melanoma. GNAQ/GNA11 mutations were characterized in archived tumor tissue. Using a highly sensitive and mutation-specific bidirectional pyrophosphorolysis-activated polymerization (bi-PAP) technique, GNAQ c.626^a>T, GNAQ c.626^a>C and GNA11 c.626^a>T copy numbers were quantified in plasma from 12 mL of blood. CTCs were detected at the same time in 7.5 mL of blood by the CellSearch[®] technique. Patient characteristics and outcome were prospectively collected. CTCs (>/=1) were detected in 12 of the 40 included patients (30%, range 1-20). Among the 26 patients with known detectable mutations, ctDNA was detected and quantified in 22 (84%, range 4-11,421 copies/mL). CTC count and ctDNA levels were associated with the presence of miliary hepatic metastasis (p = 0.004 and 0.03, respectively), with metastasis volume (p = 0.005 and 0.004) and with each other (p < 0.0001). CTC count and ctDNA levels were both strongly associated with progression-free survival (p = 0.003 and 0.001) and overall survival (p = 0.0009 and <0.0001). In multivariate analyses, ctDNA appeared to be a better prognostic marker than CTC. In conclusion, ctDNA and CTC are correlated and both have poor prognostic significance. CTC detection can be performed in every patient but, in patients with detectable mutations, ctDNA was more frequently detected than CTC and has possibly more prognostic value.

[198]

TÍTULO / TITLE: - Immunohistochemical and FISH analysis of EGFR and its prognostic value in patients with oral squamous cell carcinoma.

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

REVISTA / JOURNAL: - J Oral Pathol Med. 2013 Sep 11. doi: 10.1111/jop.12111.

●● Enlace al texto completo (gratis o de pago) [1111/jop.12111](https://doi.org/10.1111/jop.12111)

AUTORES / AUTHORS: - Grobe A; Eichhorn W; Fraederich M; Kluwe L; Vashist Y; Wikner J; Smeets R; Simon R; Sauter G; Heiland M; Blessmann M

INSTITUCIÓN / INSTITUTION: - Department of Oral and Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

RESUMEN / SUMMARY: - OBJECTIVES: To study immunohistochemical expression of the epithelial growth factor receptor (EGFR) in oral carcinomas and the head and neck region to examine possible associations with various features of the tumors and survival of the patients. MATERIALS AND METHODS: Sections were made from two tissue arrays composed of 206 oral squamous cell carcinomas and 427 squamous cell carcinomas of the head and neck region, respectively, and examined for EGFR expression and Ki-67 labeling index by means of immunohistochemistry, and for EGFR gene amplification by means of fluorescence in situ hybridization. Correlation between resulting parameters and with clinical features was evaluated using chi-square test and Kaplan-Meier analysis. RESULTS: A statistically significant association was observed for strong EGFR immunohistochemical (IHC) expression with advanced lymph node involvement ($P = 0.02$). EGFR immunohistochemical expression did not significantly correlate with patient disease specific (DS) or overall survival (OS). EGFR gene amplification was not correlated with any of the tumor features nor to survival of the patients (DS and OS). DISCUSSION: Epithelial growth factor receptor IHC expression and gene amplification might be suitable to predict locoregional control in oral squamous cell carcinoma patients but an inappropriate predictor for patients survival.

[199]

TÍTULO / TITLE: - IL-15 gene therapy and the mTOR inhibitor everolimus inhibit growth of metastatic breast cancer.

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

REVISTA / JOURNAL: - J Gene Med. 2013 Sep 3. doi: 10.1002/jgm.2739.

●● Enlace al texto completo (gratis o de pago) [1002/jgm.2739](#)

AUTORES / AUTHORS: - Zhao N; Li X; He X; Qiu Y; Zhu L; Qi F

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Tianjin Medical University General Hospital, Tianjin, 300052, China.

RESUMEN / SUMMARY: - BACKGROUND: Novel methods to control and treat metastatic breast cancer are needed. Interleukin-15 (IL-15) is a promising cytokine for cancer immunotherapy, and everolimus is an orally administered mTOR inhibitor, which is already approved for cancer treatment. In the current study, we investigate the efficacy of IL-15 gene therapy and explore the possibility of combining IL-15 therapy with everolimus to treat metastatic breast cancer. METHODS: A plasmid encoding IL-15 and everolimus were given to mice inoculated with 4 T1 mouse breast cancer cells. Tumor size and metastasis were monitored to assess the effect of different treatment regimens. Immunohistochemistry was used to detect CD4⁺, CD8⁺, and NKG2D⁺ cells and also the expression of Ki-67 in tumor tissue; these analyses helped establish the immunization status and tumor proliferation rate of different treatment groups. TUNEL assays were performed to assess cellular apoptosis in tumor tissues. RESULTS: Both IL-15 and everolimus significantly decreased tumor size. IL-15 gene therapy increased the

proportion of CD4+ T and NK cells but had no effect on CD8+ T cells. In contrast, everolimus decreased the number of CD8+ T cells but had no effect on CD4+ T and NK cells compared to the control group. Both IL-15 and everolimus decreased expression of Ki-67 and increased rates of apoptosis. While effective on their own, no synergistic effect was observed with combined treatment of everolimus and IL-15 gene therapy. CONCLUSIONS: IL-15 gene therapy was potentially useful for the treatment of metastatic breast cancer. The possibility of combining immunotherapy with everolimus requires further investigation. This article is protected by copyright. All rights reserved.

[200]

TÍTULO / TITLE: - Biomarkers for prediction of venous thromboembolism in cancer.

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

REVISTA / JOURNAL: - Blood. 2013 Sep 19;122(12):2011-8. doi: 10.1182/blood-2013-04-460147. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-04-460147](#)

AUTORES / AUTHORS: - Pabinger I; Thaler J; Ay C

INSTITUCIÓN / INSTITUTION: - Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - Cancer patients are at increased risk of deep vein thrombosis and pulmonary embolism. The incidence among different groups of cancer patients varies considerably depending on clinical factors, the most important being tumor entity and stage. Biomarkers have been specifically investigated for their capacity of predicting venous thromboembolism (VTE) during the course of disease. Parameters of blood count analysis (elevated leukocyte and platelet count and decreased hemoglobin) have turned out to be useful in risk prediction. Associations between elevated levels and future VTE have been found for d-dimer, prothrombin fragment 1+2, and soluble P-selectin and also for clotting factor VIII and the thrombin generation potential. The results for tissue factor-bearing microparticles are heterogeneous: an association with occurrence of VTE in pancreatic cancer might be present, whereas in other cancer entities, such as glioblastoma, colorectal, or gastric carcinoma, this could not be confirmed. Risk assessment models were developed that include clinical and laboratory markers. In the high-risk categories, patient groups with up to a >20% VTE rate within 6 months can be identified. A further improvement in risk stratification would allow better identification of patients for primary VTE prevention using indirect or novel direct anticoagulants.

[201]

TÍTULO / TITLE: - Reduced expression of bone morphogenetic protein receptor IA in pancreatic cancer is associated with a poor prognosis.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Oct 1;109(7):1805-1812. doi: 10.1038/bjc.2013.486. Epub 2013 Aug 22.

●● Enlace al texto completo (gratuito o de pago) [1038/bjc.2013.486](#)

AUTORES / AUTHORS: - Voorneveld PW; Stache V; Jacobs RJ; Smolders E; Sitters AI; Liesker A; S Korkmaz K; Lam SM; De Miranda NF; Morreau H; Kodach LL; Hardwick JC

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands.

[202]

TÍTULO / TITLE: - Fractional Change in Apparent Diffusion Coefficient as an Imaging Biomarker for Predicting Treatment Response in Head and Neck Cancer Treated with Chemoradiotherapy.

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

REVISTA / JOURNAL: - AJNR Am J Neuroradiol. 2013 Sep 12.

AUTORES / AUTHORS: - Matoba M; Tuji H; Shimode Y; Toyoda I; Kuginuki Y; Miwa K; Tonami H

INSTITUCIÓN / INSTITUTION: - Departments of Radiology and Otorhinolaryngology, Kanazawa Medical University, Ishikawa, Japan.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE:ADC provides a measure of water molecule diffusion in tissue. The aim of this study was to evaluate whether the fractional change in ADC during therapy can be used as a valid predictive indicator of treatment response in head and neck squamous cell carcinoma treated with chemoradiotherapy.MATERIALS AND METHODS:Forty patients underwent DWI at pretreatment and 3 weeks after the start of treatment. The pretreatment ADC, fractional change in ADC, tumor regression rate, and other clinical variables were compared with locoregional control and locoregional failure and were analyzed by using logistic regression analysis and receiver operating characteristic analysis. Furthermore, progression-free survival curves divided by the corresponding threshold value were compared by means of the log-rank test.RESULTS:The fractional change in ADCprimary, the fractional change in ADCnode, primary tumor volume, nodal volume, tumor regression ratenode, N stage, and tumor location revealed significant differences between locoregional failure and locoregional control (P < .05). In univariate analysis, the fractional change in ADCprimary, fractional change in ADCnode, tumor regression ratenode, N stage, and tumor location showed significant association with locoregional control (P < .05). In multivariate analysis, however, only the fractional change in ADCprimary was identified as a significant and independent predictor of locoregional control (P = .04). A threshold fractional change in ADCprimary of 0.24 revealed a sensitivity of 100%, specificity of 78.7%, and overall accuracy of 84.8% for the prediction of locoregional control. Progression-free survival of the 2

groups divided by the fractional change in ADC_{primary} at 0.24 showed a significant difference ($P < .05$). CONCLUSIONS: The results suggest that the fractional change in ADC_{primary} is a valid imaging biomarker for predicting treatment response in head and neck squamous cell carcinoma treated with chemoradiotherapy.

[203]

TÍTULO / TITLE: - Toca 511 gene transfer and 5-fluorocytosine in combination with temozolomide demonstrates synergistic therapeutic efficacy in a temozolomide-sensitive glioblastoma model.

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

REVISTA / JOURNAL: - Cancer Gene Ther. 2013 Aug 23. doi: 10.1038/cgt.2013.51.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cgt.2013.51](#)

AUTORES / AUTHORS: - Huang TT; Hlavaty J; Ostertag D; Espinoza FL; Martin B; Petznek H; Rodriguez-Aguirre M; Ibanez CE; Kasahara N; Gunzburg W; Gruber HE; Pertschuk D; Jolly DJ; Robbins JM

INSTITUCIÓN / INSTITUTION: - Tocagen, San Diego, CA, USA.

RESUMEN / SUMMARY: - Toca 511 (vocimagene amiretrorepvec), an amphotropic retroviral replicating vector (RRV), can successfully and safely deliver a functional, optimized cytosine deaminase (CD) gene to tumors in orthotopic glioma models. This agent, in conjunction with subsequent oral extended-release 5-fluorocytosine (5-FC) (Toca FC), is currently under investigation in patients with recurrent high-grade glioma. Temozolomide (TMZ) with radiation is the most frequently used first-line treatment for patients with glioblastoma, the most common and aggressive form of primary brain cancer in adults. However, subsets of patients with certain genetic alterations do not respond well to TMZ treatment and the overall median survival for patients who respond remains modest, suggesting that combinatorial approaches may be necessary to significantly improve outcomes. We show that in vitro TMZ delays but does not prevent RRV spread, nor interfere with Toca 511+5-FC-mediated cell killing in glioma tumor cells, and in vivo there is no significant hematologic effect from the combination of 5-FC and the clinically relevant dose of TMZ. A synergistic long-term survival advantage is observed in mice bearing an orthotopic TMZ-sensitive glioma after Toca 511 administration followed by coadministration of TMZ and 5-FC. These results provide support for the investigation of this novel combination treatment strategy in patients with newly diagnosed malignant glioma. Cancer Gene Therapy advance online publication, 23 August 2013; doi:10.1038/cgt.2013.51.

[204]

TÍTULO / TITLE: - Correlation and prognostic value of osteopontin and Bcl-2 in hepatocellular carcinoma patients after curative resection.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Sep 19. doi: 10.3892/or.2013.2737.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2737](#)

AUTORES / AUTHORS: - Deng B; Zhang XF; Zhu XC; Huang H; Jia HL; Ye QH; Dong QZ; Qin LX

INSTITUCIÓN / INSTITUTION: - Liver Cancer Institute and Zhongshan Hospital, Institutes of Biomedical Sciences, Fudan University, Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai 200032, P.R. China.

RESUMEN / SUMMARY: - Osteopontin (OPN) may facilitate tumorigenesis and metastasis through prevention of tumor cells from apoptosis. Although previous studies have suggested involvement of enhanced Bcl-2 protein family expression, the role of OPN together with Bcl-2 in hepatocellular carcinoma (HCC) remains unknown. In this study, we used western blotting to detect the OPN and Bcl-2 expression levels in cell lines with different OPN backgrounds and HCC tissues, and tumor tissue microarrays to examine OPN and Bcl-2 expression levels in 454 HCC cases. The Kaplan-Meier method and log-rank test were applied to investigate the predictive values of OPN and Bcl-2 in HCC patients. In vitro assays indicated that OPN expression increased concordantly with increasing metastatic potential in MHCC97-H, MHCC97-L, HepG2 and SMMC-7721 cell lines by western blotting, whereas Bcl-2 expression declined. In addition, Bcl-2 was highly upregulated in OPN knockdown MHCC97-H cell lines. Furthermore, in HCC tissues, it was confirmed that OPN levels were also significantly higher in recurrent tumor tissues compared to non-recurrent tissues by western blotting ($p < 0.001$), whereas the contrary occurred in Bcl-2 ($p = 0.046$). Using immunohistochemistry analysis, patients with higher OPN levels had significantly shorter median survival time and recurrence time compared to the lower ones, although the opposite occurred in Bcl-2 levels. Of note, when OPN and Bcl-2 were combined, we found that the co-index of OPN/Bcl-2 was an independent prognostic factor for both overall survival ($p < 0.001$) and time to recurrence ($p < 0.001$). Our findings demonstrate that OPN/Bcl-2 expression is a promising independent predictor of recurrence and survival in HCC. Additionally, Bcl-2 levels may be regulated by OPN in the HCC microenvironment.

[205]

TÍTULO / TITLE: - Prognostic Role of Serum Lactate Dehydrogenase Beyond Initial Diagnosis: A Retrospective Analysis of Patients with Diffuse Large B Cell Lymphoma.

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

REVISTA / JOURNAL: - Acta Haematol. 2013 Aug 31;130(4):305-311.

●● Enlace al texto completo (gratis o de pago) [1159/000353127](#)

AUTORES / AUTHORS: - Hong J; Yoon HH; Ahn HK; Sym SJ; Park J; Park PW; Ahn JY; Park S; Cho EK; Shin DB; Lee JH

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Gachon University School of Medicine, Incheon, Republic of Korea.

RESUMEN / SUMMARY: - Background/Aims: Baseline serum lactate dehydrogenase (LDH) level is a well-known prognostic factor in patients with non-Hodgkin's lymphoma; however, its role beyond initial diagnosis has not yet been defined. Methods: This study was conducted as a retrospective analysis of patients with diffuse large B cell lymphoma (DLBCL) treated with R-CHOP21, who had undergone regular checks for LDH during immunochemotherapy (n = 119) and during the posttreatment follow-up period after complete remission (CR; n = 100). The 119 patients were classified into 4 groups according to their baseline and change in LDH level during treatment, and an analysis of tumor response and survival was performed. The value of LDH as a predictor for relapse was evaluated among the patients with regular follow-up visits after achieving CR. Results: An increased LDH level during immunochemotherapy had no impact on tumor response or survival, and only the LDH status 'before' treatment was a prognostic marker. The sensitivity, specificity, positive predictive value and negative predictive value of serum LDH for detecting relapse after CR were 47.4, 86.5, 9.3 and 98.3%, respectively. Conclusion: The measurement of LDH level beyond initial diagnosis has no clear benefit in predicting disease progression or relapse in patients with DLBCL treated with R-CHOP21.

[206]

TÍTULO / TITLE: - Personalized medicine in breast cancer: tamoxifen, endoxifen, and CYP2D6 in clinical practice.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2700-1](#)

AUTORES / AUTHORS: - Ruddy KJ; Desantis SD; Gelman RS; Wu AH; Punglia RS; Mayer EL; Tolaney SM; Winer EP; Partridge AH; Burstein HJ

INSTITUCIÓN / INSTITUTION: - Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA, 02215, USA, kathryn_ruddy@dfci.harvard.edu.

RESUMEN / SUMMARY: - Tamoxifen is metabolized into endoxifen, a potent antagonist of the estrogen receptor, in part through cytochrome p450 (CYP) 2D6. Genotypic variation in CYP2D6 affects endoxifen levels, and some have argued that patients who do not efficiently metabolize tamoxifen might wish to consider alternative hormonal treatments. This study evaluated an algorithm in which endoxifen levels and CYP2D6 genotypes were used to make hormonal therapy recommendations for patients on adjuvant tamoxifen for breast cancer. Patients with stage I-III breast cancer who had been taking adjuvant tamoxifen for 8-56 weeks were eligible. At enrollment, baseline whole blood and serum were sent for genotyping by Amplichip and endoxifen measurement, respectively, and endoxifen levels were also measured 3 weeks later.

Results were returned to oncologists along with an algorithm-generated treatment recommendation. The algorithm recommended that participants with poor metabolizer genotype and/or baseline endoxifen level <6 ng/mL consider alternative endocrine therapy. A medical record review evaluated actual treatment decisions. Of 99 patients on study, 18 (18 %) had findings that triggered algorithm-based recommendations to consider a change in endocrine therapy due to endoxifen <6 ng/mL (all 18 patients) and/or poor metabolizer CYP2D6 genotype (2 of the 18). Endoxifen levels were ≥ 6 ng/mL in four of them 3 weeks later. Seven (39 % of 18) switched to a different treatment (one based on toxicity, not the algorithm). Hot flash burden was not found to be significantly associated with endoxifen <6 ng/mL or genotype. Prospective testing of tamoxifen metabolism as gauged by CYP2D6 genotype and serum endoxifen levels is feasible. Future studies of tamoxifen metabolism and efficacy should consider including measurement of serial endoxifen levels. Although clinical evidence at present is insufficient to warrant routine CYP2D6 or endoxifen testing, some clinicians and patients did utilize this predefined algorithm to inform clinical decisions regarding optimal adjuvant endocrine therapy.

[207]

TÍTULO / TITLE: - Glutathione transferase-A2 S112T polymorphism predicts survival, transplant-related mortality, busulfan and bilirubin blood levels after allogeneic stem cell transplantation.

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

REVISTA / JOURNAL: - Haematologica. 2013 Sep 20.

●● [Enlace al texto completo \(gratis o de pago\) 3324/haematol.2013.089888](#)

AUTORES / AUTHORS: - Bonifazi F; Storci G; Bandini G; Marasco E; Dan E; Zani E; Albani F; Bertoni S; Bontadini A; De Carolis S; Sapienza MR; Rizzi S; Ferioli M; Garagnani P; Cavo M; Mantovani V; Bonafe M

INSTITUCIÓN / INSTITUTION: - University of Bologna, Italy;

RESUMEN / SUMMARY: - Busulfan liver metabolism depends on glutathione, a crucial mediator of cellular and systemic stress. Here we investigated 40 polymorphisms at 27 loci involved in hepatic glutathione homeostasis, with the aim to test their impact on the clinical outcome of 185 busulfan-conditioned allogeneic transplants. GSTA2 S112T serine allele homozygosity is an independent prognostic factor for poorer survival (RR=2.388), for increased any time- and 100-day Transplant Related Mortality (RR=4.912 and RR=5.185, respectively). The genotype also predicts a wider busulfan area under the concentration-time curve (1214.36+570.06 vs 838.10+282.40 $\mu\text{Mol}\cdot\text{min}$) and higher post-transplant bilirubin serum levels (3.280+0.422 vs 1.874+0.197 mg/dL). In vitro, busulfan elicits pro-inflammatory activation (increased NF-KappaB activity and interleukin-8 expression) in human hepatoma cells. At the same time, the drug down-regulates a variety of genes involved in bilirubin liver

clearance: constitutive androstane receptor, multidrug resistance-associated protein, solute carrier organic anion transporters, and even GSTA2. Worthy of note, is the fact that GSTA2 also acts as an intra-hepatic bilirubin binding protein. These data underline the prognostic value of GSTA2 genetic variability in busulfan-conditioned allotransplants and suggest a patho-physiological model in which busulfan-induced inflammation leads to the impairment of post-transplant bilirubin metabolism.

[208]

TÍTULO / TITLE: - FRAX597, a small molecule inhibitor of the p21-activated kinases, inhibits tumorigenesis of NF2-associated schwannomas.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Aug 19.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.510933](https://doi.org/10.1074/jbc.M113.510933)

AUTORES / AUTHORS: - Licciulli S; Maksimoska J; Zhou C; Troutman S; Kota S; Liu Q; Duron S; Campbell D; Chernoff J; Field J; Marmorstein R; Kissil JL

INSTITUCIÓN / INSTITUTION: - The Scripps Research Institute, United States;

RESUMEN / SUMMARY: - The p21-activated kinases (PAKs) are immediate downstream effectors of the Rac/Cdc42 small G-proteins and implicated in promoting tumorigenesis in various type of cancer including breast and lung carcinomas. Recent studies have established a requirement for the PAKs in the pathogenesis of Neurofibromatosis type 2 (NF2), a dominantly inherited cancer disorder caused by mutations at the NF2 gene locus. Merlin, the protein product of the NF2 gene, has been shown to negatively regulate signaling through the PAKs and the tumor suppressive functions of Merlin are mediated, at least in part, through inhibition of the PAKs. Knockdown of PAK1 and PAK2 expression, through RNAi-based approaches, impairs the proliferation of NF2-null schwannoma cells in culture and inhibits their ability to form tumors in vivo. These data implicate the PAKs as potential therapeutic targets. High-throughput screening of a library of small molecules combined with a structure-activity relationship approach resulted in the identification of FRAX597, a small-molecule pyridopyrimidinone, as a potent inhibitor of the group I PAKs. Crystallographic characterization of the FRAX597/PAK1 complex identifies a phenyl ring that traverses the gatekeeper residue and positions the thiazole in the back cavity of the ATP binding site, a site rarely targeted by kinase inhibitors. FRAX597 inhibits the proliferation of NF2-deficient schwannoma cells in culture and displayed potent anti-tumor activity in vivo, impairing schwannoma development in an orthotopic model of NF2. These studies identify a novel class of orally available ATP-competitive Group I PAK inhibitors with significant potential for the treatment of NF2 and other cancers.

[209]

TÍTULO / TITLE: - Antiproliferative and Proapoptotic Activity of Sunitinib on Endothelial and Anaplastic Thyroid Cancer Cells via Inhibition of Akt and ERK1/2 Phosphorylation and by Down-Regulation of Cyclin-D1.

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

REVISTA / JOURNAL: - J Clin Endocrinol Metab. 2013 Sep;98(9):E1465-73. doi: 10.1210/jc.2013-1364. Epub 2013 Aug 22.

●● [Enlace al texto completo \(gratuito o de pago\) 1210/jc.2013-1364](#)

AUTORES / AUTHORS: - Di Desidero T; Fioravanti A; Orlandi P; Canu B; Giannini R; Borrelli N; Man S; Xu P; Fontanini G; Basolo F; Kerbel RS; Francia G; Danesi R; Bocci G

INSTITUCIÓN / INSTITUTION: - MD, PhD, Division of Pharmacology, Department of Clinical and Experimental Medicine, University of Pisa, and Istituto Toscano Tumori, Via Roma, 55, 56126 Pisa, Italy. guido.bocci@med.unipi.it.

RESUMEN / SUMMARY: - Context: Recent experimental evidence suggests a rationale for the use of multitarget tyrosine kinase inhibitors for the treatment of thyroid cancers. Sunitinib showed promising preliminary results against anaplastic thyroid cancer (ATC), and it has been used for some patients who are ineligible for clinical trials. Objectives: The aims of this study were to investigate the in vitro and in vivo activity of sunitinib on ATC and on microvascular endothelial cells and the molecular mechanism for the observed sunitinib activity. Methods: Proliferation and apoptotic assays were performed on human dermal microvascular endothelial and on BRAF- or H-ras-mutated ATC cells (8305C and FB3, respectively) after in vitro exposure to sunitinib for 72 hours. Vascular endothelial growth factor receptor-2, epithelial growth factor receptor, ERK1/2, and Akt phosphorylation was quantified by ELISA and Western blot. Cyclin-D1 mRNA expression was evaluated by real-time PCR, and cyclin-D1 intracellular concentrations were measured by ELISA. 8305C tumor xenografts in nude mice were treated with sunitinib at 50 mg/kg/d (ip). Results: Antiproliferative and proapoptotic activity of sunitinib was observed in both endothelial and ATC cells. Phospho-vascular endothelial growth factor receptor-2 levels significantly decreased after sunitinib treatment in activated endothelial cells. Phospho-epidermal growth factor receptor, ERK1/2, and Akt phosphorylation was significantly inhibited by sunitinib treatment in endothelial and cancer cells, and cyclin-D1 mRNA and protein expression was inhibited. Sunitinib administration in vivo caused significant inhibition of tumor growth ($P < .05$). Conclusions: Sunitinib is active in vitro and in vivo against activated endothelial and ATC cells via the inhibition of Akt and ERK1/2 phosphorylation and through the down-regulation of cyclin-D1.

[210]

TÍTULO / TITLE: - Combined epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor and chemotherapy in non-small-cell lung cancer: Chemo-refractoriness of cells harboring sensitizing-EGFR mutations in the presence of gefitinib.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Sep 8. pii: S0169-5002(13)00393-0. doi: 10.1016/j.lungcan.2013.08.028.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.08.028](#)

AUTORES / AUTHORS: - Tsai CM; Chen JT; Chiu CH; Lai CL; Hsiao SY; Chang KT

INSTITUCIÓN / INSTITUTION: - Division of Thoracic Oncology, Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan. Electronic address: doc3006a@gmail.com.

RESUMEN / SUMMARY: - BACKGROUND: Combined epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) with chemotherapy is believed to be more effective in treating non-small-cell lung cancer (NSCLC) with sensitizing-EGFR mutation (SEM). This hypothesis failed to be realized clinically and needs to be examined in vitro. MATERIALS AND METHODS: Using the tetrazolium colorimetric assay and classical isobole method, we investigated the combination effects of 6 gefitinib-chemotherapeutic doublets (gefitinib/cisplatin, gemcitabine, pemetrexed, paclitaxel, docetaxel, or vinorelbine) in a panel of 15 NSCLC cell lines. RESULTS: Upon treatment with the 6 gefitinib-chemotherapeutic doublets, the 12 cell lines that did not harbor SEM displayed a broad spectrum of group results, from obvious synergism to robust antagonism. The values of group mean combination index (mCIs) ranged from 0.769 to 1.201. In contrast, the 3 cell lines with SEM showed a tendency toward consistent antagonism to the tested doublets, impressively, with a narrow range of higher group mCIs (0.993-1.141). In the presence of gefitinib, the SEM or gefitinib-sensitive group was more chemo-refractory than the non-SEM (index of chemo-refractoriness (RI): 69.33 versus 42.67; P=0.036) or gefitinib-resistant group (68.25 versus 40.64, P=0.0108), respectively. The results of using the gefitinib/drug combinations with the gefitinib-sensitive non-SEM cell line H322 and the gefitinib-resistant EGFR mutant H820 shared patterns similar to those with the SEM and non-SEM cell lines, respectively. CONCLUSION: Gefitinib-treated EGFR-TKI-sensitive NSCLC cells showed a wide spectrum of chemo-refractoriness, suggesting that concomitantly combined EGFR-TKI-chemotherapy might not be a good treatment strategy for NSCLC harboring SEM.

[211]

TÍTULO / TITLE: - Margin Infiltrating CD20+ B Cells Display an Atypical Memory Phenotype and Correlate with Favorable Prognosis in Hepatocellular Carcinoma.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3497](#)

AUTORES / AUTHORS: - Shi JY; Gao Q; Wang ZC; Zhou J; Wang X; Min ZH; Shi YH; Shi GM; Ding ZB; Ke AW; Dai Z; Qiu SJ; Song K; Fan J

INSTITUCIÓN / INSTITUTION: - Department of Liver surgery, Liver Cancer Institute, Zhong Shan Hospital and Shanghai Medical School, Fudan University.

RESUMEN / SUMMARY: - **PURPOSE:** The role of infiltrating B cells in hepatocellular carcinoma (HCC) has been overlooked for many years. This study is aimed to delineate the distribution, prognostic value and functional status of B cells in human HCC. **EXPERIMENTAL DESIGN:** Immunohistochemistry was used to investigate the distribution and clinical significance of infiltrating CD20+ B cells in a series of 120 HCC patients. The results were further tested in an independent series of 200 HCC patients. The functional status of CD20+ B cells was determined by flow cytometry, immunofluorescence and in vitro co-culture assay. **RESULTS:** Infiltrating CD20+ B cells were predominantly concentrated in the tumor invasive margin, compared to the peri-tumor and intra-tumor areas. High density of margin infiltrating B cells (MIL-Bs) positively correlated with small tumor size, absence of vascular invasion and increased density of CD8+ T cells ($P < 0.05$). Survival analyses revealed that increased MIL-Bs and their penetration through the tumor capsule were significantly associated with improved overall and recurrence-free survival, and were identified as independent prognosticators for HCC patients ($P < 0.05$). Importantly, the results were further validated in another independent HCC cohort. Moreover, we found that MIL-Bs featured an atypical memory phenotype (IgD-IgG+CD27-CD38-), expressed surface markers characteristic of antigen-presenting cells, possessed tumor-killing potential by producing IFN-gamma, IL-12p40, granzyme B, TRAIL, and acted in cooperation with CD8+ T cells. **CONCLUSIONS:** The profile of CD20+ B cells in situ is a new predictor of prognosis for HCC patients and provides a novel target for an optimal immunotherapy against this fatal malignancy.

[212]

TÍTULO / TITLE: - Cyclin-dependent kinase 5 modulates STAT3 and androgen receptor activation through phosphorylation of Ser727 on STAT3 in prostate cancer cells.

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

REVISTA / JOURNAL: - Am J Physiol Endocrinol Metab. 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1152/ajpendo.00615.2012](#)

AUTORES / AUTHORS: - Hsu FN; Chen MC; Lin KC; Peng YT; Li PC; Lin E; Chiang MC; Hsieh JT; Lin H

INSTITUCIÓN / INSTITUTION: - 1National Chung Hsing University.

RESUMEN / SUMMARY: - Cyclin-dependent kinase 5 (Cdk5) is known to regulate prostate cancer metastasis. Our previous results indicate that Cdk5 activates androgen receptor (AR) and supports prostate cancer growth. We also find that STAT3 is a target of Cdk5 in promoting thyroid cancer cell growth, while STAT3 may play a regulator to AR

activation under cytokine control. This study is to investigate the regulation of Cdk5 and its activator p35 on STAT3/AR signaling in prostate cancer cells. Our results show that Cdk5 biochemically interacts with STAT3 and this interaction depends on Cdk5 activation in prostate cancer cells. The phosphorylation of STAT3 at serine-727 (p-S727-STAT3) is regulated by Cdk5 in cells and xenograft tumors. The mutant of STAT3 S727A reduces its interaction with Cdk5. We further show that the nuclear distribution of p-S727-STAT3 and the expression of STAT3-regulated genes (junB, c-fos, c-myc and survivin) are regulated by Cdk5 activation. STAT3 mutant does not further decrease cell proliferation upon Cdk5 inhibition, which implies that the role of STAT3 regulated by Cdk5 correlates to cell proliferation control. Interestingly, Cdk5 may regulate the interaction between STAT3 and AR through phosphorylation of S727-STAT3 and therefore up-regulate AR protein stability and transactivation. Correspondingly, clinical evidence shows that the level of p-S727-STAT3 is significantly correlated with Gleason score and the levels of upstream regulators (Cdk5 and p35) as well as downstream protein (AR). In conclusion, this study demonstrates that Cdk5 regulates STAT3 activation through S727 phosphorylation and further promotes AR activation by protein-protein interaction in prostate cancer cells.

[213]

TÍTULO / TITLE: - Real Time Analysis of Binding between Rituximab (Anti-CD20 Antibody) and B Lymphoma Cells.

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

REVISTA / JOURNAL: - Anal Chem. 2013 Sep 17;85(18):8543-51. doi: 10.1021/ac400062v. Epub 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [1021/ac400062v](#)

AUTORES / AUTHORS: - Tan L; Lin P; Chisti MM; Rehman A; Zeng X

INSTITUCIÓN / INSTITUTION: - Chemistry Department, Oakland University , Rochester, Michigan 48309, United States.

RESUMEN / SUMMARY: - CD20, expressed on greater than 90% of B-lymphocytic lymphomas, is an attractive target for antibody therapy. Rituximab is a chimeric murine/human-engineered monoclonal antibody which can selectively deplete CD20-expressing cells in peripheral blood and lymphoid tissues. The immobilization of B-lymphoblast-like Burkitt's lymphoma Raji cells on the quartz crystal microbalance (QCM) gold electrode surface using arginine-glycine-aspartic acid (RGD) tripeptide was electrochemically confirmed. The real-time processes of attachment of Raji cells on the gold electrode and the subsequent binding of Rituximab to the cells were studied using a QCM biosensor. The interaction between Rituximab and Raji cells led to the increased resonant frequency shifts (Δf_0) in the studied antibody concentration range from 5 to 250 $\mu\text{g mL}^{-1}$ following the Langmuir adsorption model. From these observations, the apparent binding constant between a single-layer of Rituximab and

Raji cells was calculated to be $1.6 \times 10(6) M(-1)$. Control experiments using other therapeutic antibodies (i.e., Trastuzumab and Bevacizumab) and different cells (i.e., T cells and endothelial cells) proved the specific interaction between Rituximab and B cells. The effects of $Ca(2+)$ and $Mn(2+)$ ions on the Rituximab-Raji cell interaction were also studied providing the enhanced QCM signals, in particular with $Ca(2+)$, further indicating that CD20 is a calcium ion channel that can transport these metal ions into the cells and accelerate the cell lysis induced by Rituximab. Thus, the real time capability of QCM and its simplicity of operation are shown to be highly suitable for multipurpose studies on living cells including cell-immobilization, cytotoxicity of drugs, and the cell action mechanisms.

[214]

TÍTULO / TITLE: - Clinical significance of serum soluble interleukin-2 receptor-alpha in extranodal natural killer/T-cell lymphoma (ENKTL): a predictive biomarker for treatment efficacy and valuable prognostic factor.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):723. doi: 10.1007/s12032-013-0723-4. Epub 2013 Sep 15.

●● Enlace al texto completo (gratuito o de pago) [1007/s12032-013-0723-4](#)

AUTORES / AUTHORS: - Liang W; Ding-Zhun L; Jing Z; Zhong-Jun X; Xiong-Wen P; Yue L

INSTITUCIÓN / INSTITUTION: - Department of Hematological Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, 510060, People's Republic of China.

RESUMEN / SUMMARY: - Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL) is an aggressive disease, and no standard treatment and validated prognostic model were established. Serum sIL-2Ralpha levels were measured in 94 ENKTL patients to evaluate its relationship with clinical features, treatment response, and prognosis. Serum sIL-2Ralpha level was 2964 ± 1613.6 ng/L in ENKTL patients, higher than in normal healthy controls ($p < 0.05$). Using median level (2508.5 ng/L) as cutoff, patients were divided into higher- and lower-level group ($N = 47$ for each). The complete remission and overall remission rate were significantly higher in lower-level group ($p < 0.05$). After a median follow-up time of 22.0 months, 2-year overall survival and progression-free survival rates were 60.0 and 53.0 %, respectively. Lower sIL-2Ralpha level significantly correlated with better progression-free survival (PFS) and overall survival (OS) ($p = 0.001$ and 0.002 , respectively). IPI score and treatment responses after 2 cycles of chemotherapy significantly correlated with PFS and OS ($p < 0.05$). In a multivariate Cox regression model that included IPI score, treatment responses, and sIL-2Ralpha level, all three parameters were independent prognostic factors for OS ($p = 0.043$, 0.001 , and 0.025 , respectively), and the last two parameters were also independent factors for PFS ($p = 0.005$ and 0.005 , respectively). Elevated serum sIL-2Ralpha level was related to poor responses to treatments and can be used as a

valuable biomarker for disease activity. Moreover, serum sIL-2Ralpha was an independent prognostic factor for both OS and PFS. These results need to be validated in prospective trials and may support the incorporation of anti-CD25 targeted therapy into the treatment realm of ENKTL.

[215]

TÍTULO / TITLE: - Antiestrogen-binding site ligands induce autophagy in myeloma cells that proceeds through alteration of cholesterol metabolism.

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

REVISTA / JOURNAL: - Oncotarget. 2013 Jun;4(6):911-22.

AUTORES / AUTHORS: - Sola B; Poirot M; de Medina P; Bustany S; Marsaud V; Silvente-Poirot S; Renoir JM

INSTITUCIÓN / INSTITUTION: - Normandie University, UNICAEN EA4652, Caen, France.

RESUMEN / SUMMARY: - Multiple myeloma (MM) is a malignancy characterized by the accumulation of clonal plasma cells in the bone marrow. Despite extensive efforts to design drugs targeting tumoral cells and their microenvironment, MM remains an incurable disease for which new therapeutic strategies are needed. We demonstrated here that antiestrogens (AEs) belonging to selective estrogen receptor modulators family induce a caspase-dependent apoptosis and trigger a protective autophagy. Autophagy was recognized by monodansylcadaverin staining, detection of autophagosomes by electronic microscopy, and detection of the cleaved form of the microtubule-associated protein light chain 3. Moreover, autophagy was inhibited by drugs such as bafilomycin A1 and 3-methyladenosine. Autophagy was mediated by the binding of AEs to a class of receptors called the antiestrogen binding site (AEBS) different from the classical estrogen nuclear receptors. The binding of specific ligands to the AEBS was accompanied by alteration of cholesterol metabolism and in particular accumulation of sterols: zymostenol or desmosterol depending on the ligand. This was due to the inhibition of the cholesterol-5,6-epoxide hydrolase activity borne by the AEBS. We further showed that the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin pathway mediated autophagy signaling. Moreover, AEBS ligands restored sensitivity to dexamethasone in resistant MM cells. Since we showed previously that AEs arrest MM tumor growth in xenografted mice, we propose that AEBS ligands may have a potent antimyeloma activity alone or in combination with drugs used in clinic.

TÍTULO / TITLE: - Simvastatin-induced up-regulation of gap junctions composed of connexin 43 sensitize Leydig tumor cells to etoposide: An involvement of PKC pathway.

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

REVISTA / JOURNAL: - Toxicology. 2013 Oct 4;312C:149-157. doi: 10.1016/j.tox.2013.08.013. Epub 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) 1016/j.tox.2013.08.013

AUTORES / AUTHORS: - Wang L; Fu Y; Peng J; Wu D; Yu M; Xu C; Wang Q; Tao L

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou 510080, People's Republic of China; Department of Anesthesia, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510260, People's Republic of China.

RESUMEN / SUMMARY: - Some of lipophilic statins have been reported to enhance toxicities induced by antineoplastic agents but the underlying mechanism is unclear. The authors investigated the involvement of Cx43-mediated gap junction intercellular communication (GJIC) in the effect of simvastatin on the cellular toxicity induced by etoposide in this study. The results showed that a major component of the cytotoxicity of therapeutic levels of etoposide is mediated by gap junctions composed of connexin 43 (Cx43) and simvastatin at the dosage which does not induce cytotoxicity enhances etoposide toxicity by increasing gap junction coupling. The augmentative effect of simvastatin on GJIC was related to the inhibition of PKC-mediated Cx43 phosphorylation at ser368 and subsequent enhancement of Cx43 membrane location induced by the agent. The present study suggests the possibility that upregulation of gap junctions may be utilized to increase the efficacy of anticancer chemotherapies.

[216]

TÍTULO / TITLE: - Up-regulated autocrine VEGF/VEGFR-2 loop prevents apoptosis in hemangioma-derived endothelial cells.

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

REVISTA / JOURNAL: - Br J Dermatol. 2013 Aug 19. doi: 10.1111/bjd.12592.

●● [Enlace al texto completo \(gratis o de pago\) 1111/bjd.12592](#)

AUTORES / AUTHORS: - Ji Y; Chen S; Li K; Xiao X; Zheng S

INSTITUCIÓN / INSTITUTION: - Division of Oncology, Department of Pediatric Surgery, Children's Hospital of Fudan University, Shanghai, 201102, China.

RESUMEN / SUMMARY: - **BACKGROUND:** The autocrine vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)-2 loop is required to maintain the transformed phenotype of many tumors, in part, by preventing apoptotic cell death in response to many different stimuli. However, it is unclear whether constitutive VEGF/VEGFR-2 activation in hemangioma-derived endothelial cells (HemECs) can lead to a general suppression of apoptosis. **OBJECTIVES:** The objective of this study was to investigate whether the autocrine VEGF loop promotes HemEC survival via its receptor, VEGFR-2. **METHODS:** HemECs and human umbilical vein endothelial cells (HUVECs) were serum-starved for 12 to 48 h. Cell apoptosis was measured. The potential mechanisms of VEGF/VEGFR-2-induced HemEC survival were investigated, and the role of the autocrine VEGF/VEGFR-2 loop in preventing propranolol-induced apoptotic HemEC death was also analyzed. **RESULTS:** Compared with HUVECs, HemECs showed increased resistance to apoptosis induced by serum starvation. Up-regulated VEGF/VEGFR-2

signaling in HemECs induced an autocrine signaling loop, which resulted in Akt activation. Furthermore, this activation of Akt was necessary for VEGF/VEGFR-2-induced protection against serum deprivation-induced HemEC apoptosis. In addition, Bcl-2, which functions as an anti-apoptotic factor and direct downstream target of PI3K/Akt, was decreased by the inhibition of VEGF/VEGFR-2, which led to an increase in caspase-3 activity, caspase-9 activity and HemEC apoptosis. Moreover, HemECs acquired greater resistance to propranolol treatment than HUVECs, whereas inhibition of VEGF/VEGFR-2 signaling in HemECs sensitized these cells to propranolol-induced apoptosis. CONCLUSIONS: Our results demonstrate that up-regulation of the autocrine VEGF/VEGFR-2 loop can induce general resistance to apoptotic stimuli in HemECs. This article is protected by copyright. All rights reserved.

[217]

TÍTULO / TITLE: - Role of glycosylation in the anticancer activity of antibacterial peptides against breast cancer cells.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Aug 17. pii: S0006-2952(13)00494-2. doi: 10.1016/j.bcp.2013.08.008.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bcp.2013.08.008](#)

AUTORES / AUTHORS: - Han YY; Liu HY; Han DJ; Zong XC; Zhang SQ; Chen YQ

INSTITUCIÓN / INSTITUTION: - Jiangsu Province Key Laboratory for Molecular and Medical Biotechnology, Life Sciences College, Nanjing Normal University, Nanjing 210000, China.

RESUMEN / SUMMARY: - Antibacterial peptides (ABPs) with cancer-selective toxicity have received much more attention as alternative chemotherapeutic agents in recent years. However, the basis of their anticancer activity remains unclear. The modification of cell surface glycosylation is a characteristic of cancer cells. The present study investigated the effect of glycosylation, in particular sialic acid, on the anticancer activity of ABPs. We showed that aurein 1.2, buforin IIb and BMAP-28m exhibited selective cytotoxicity toward MX-1 and MCF-7 breast cancer cells. The binding activity, cytotoxicity and apoptotic activity of ABPs were enhanced by the presence of O-, N-glycoproteins, gangliosides and sialic acid on the surface of breast cancer cells. Among N-, O-glycoproteins and ganglioside, O-glycoproteins almost had the strongest effect on the binding and cytotoxicity of the three peptides. Further, up-regulation of hST6Gal1 in CHO-K1 cells enhanced the susceptibility of cells to these peptides. Finally, the growth of MX-1 xenograft tumors in mice was significantly suppressed by buforin IIb treatment, which was associated with induction of apoptosis and inhibition of vascularization. These data demonstrate that the three peptides bind to breast cancer cells via an interaction with surface O-, N-glycoproteins and gangliosides. Sialic acids act as key glycan binding sites for cationic ABP binding to glycoproteins and

gangliosides. Therefore, glycosylation in breast cancer cells plays an important role in the anticancer activity of ABPs, which may partly explain their cancer-selective toxicity. Anticancer ABPs with cancer-selective cytotoxicity will be promising candidates for anticancer therapy in the future.

[218]

TÍTULO / TITLE: - Recurrent high-grade glioma treated with bevacizumab: prognostic value of MGMT methylation, EGFR status and pretreatment MRI in determining response and survival.

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

REVISTA / JOURNAL: - J Neurooncol. 2013 Aug 22.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11060-013-1225-0](#)

AUTORES / AUTHORS: - Chen C; Huang R; Maclean A; Muzikansky A; Mukundan S; Wen PY; Norden AD

INSTITUCIÓN / INSTITUTION: - Harvard Medical School, 250 Longwood Avenue, Boston, MA, 02115, USA.

RESUMEN / SUMMARY: - Although bevacizumab represented an important advance in treatment of recurrent high-grade gliomas (HGG), responses occur in fewer than half of patients. There are no validated biomarkers for anti-angiogenic therapy that are available for routine clinical use. We assessed the prognostic values of imaging and molecular markers in this patient population. MRI scans from 191 patients with recurrent HGG obtained prior to initiating bevacizumab were reviewed for areas of enhancement, necrosis, T2/FLAIR abnormality, and ADC values. Serial MRI scans following the initiation of bevacizumab were evaluated for response and progression. Non-radiographic markers including EGFR and MGMT status were also assessed with respect to response and patient survival. 65 of 191 patients (34 %) showed complete or partial response at the time of their best response MRI and demonstrated longer progression free survival (PFS) and overall survival (OS) compared to the group without response (PFS: 6.9 vs 3.5 months, OS: 10.9 vs 6.1 months). Minimum ADC values within enhancing and non-enhancing regions were lower in responders compared to those of non-responders (1,099 vs 984 x 10⁻⁶ mm²/s, p = 0.006). Smaller enhancing area was associated with longer OS (HR = 1.99, p = 0.017). The ratio of T2/FLAIR to enhancing area was prognostic of OS for only the Grade III HGG subgroup (HR = 0.14, p = 0.004). Area of enhancing tumor at baseline can stratify survival in patients with recurrent HGG treated with bevacizumab. The extent of edema relative to enhancing area may have a prognostic role specific to Grade III HGG.

[219]

TÍTULO / TITLE: - CX-4945, a selective inhibitor of casein kinase-2 (CK2), exhibits anti-tumor activity in hematologic malignancies including enhanced activity in chronic lymphocytic leukemia when combined with fludarabine and inhibitors of the B-cell receptor pathway.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jul 31. doi: 10.1038/leu.2013.228.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.228](#)

AUTORES / AUTHORS: - Prins RC; Burke RT; Tyner JW; Druker BJ; Loriaux MM; Spurgeon SE

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Medical Oncology, Oregon Health & Science University, Portland, OR, USA.

[220]

TÍTULO / TITLE: - Notch-1 contributes to epidermal growth factor receptor tyrosine kinase inhibitor acquired resistance in non-small cell lung cancer in vitro and in vivo.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 2. pii: S0959-8049(13)00556-X. doi: 10.1016/j.ejca.2013.07.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.07.007](#)

AUTORES / AUTHORS: - Xie M; He CS; Wei SH; Zhang L

INSTITUCIÓN / INSTITUTION: - China State Key Laboratory of Respiratory Disease and Guangzhou Institute of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Road, Guangzhou 510120, China. Electronic address: mianxie@gird.cn.

RESUMEN / SUMMARY: - Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) occurs in non-small cell lung cancer (NSCLC) patients who initially respond to TKI treatment but whose cancer then progresses. Recent studies have shown that Notch signal is associated with drug resistance. However, the exact mechanism of Notch during acquisition of resistance to EGFR-TKI in human lung cancer remains unclear. In the present study, we showed that the expression of Notch-1 was highly upregulated in EGFR-TKI acquired resistant lung cancer cells. More importantly, Notch-1 contributed to the acquisition of the epithelial-mesenchymal transition (EMT) phenotype, which was critically associated with acquired resistance to EGFR-TKI. Silencing of Notch-1 using siRNA resulted in mesenchymal-epithelial transition (MET), which was associated with impaired invasion and anchorage-independent growth of lung cancer and resensitisation to gefitinib in acquired resistant NSCLC cells. Finally, gefitinib treatment of Balb/c nu/nu with acquired resistant lung cancer xenografts in combination with Notch inhibitor N-[N-(3,5-difluorophenacetyl)-l-alanyl]-l-(S)-phenylglycine t-butyl ester (DAPT) resulted in effective tumour growth retardation, with decreased proliferative activity and

increased apoptotic activity. Collectively, these data suggest that Notch-1 might play a novel role in acquired resistance to gefitinib, which could be reversed by inhibiting Notch-1.

[221]

TÍTULO / TITLE: - Isocitrate dehydrogenase 1 (IDH1) mutation-specific microRNA signature predicts favorable prognosis in glioblastoma patients with IDH1 wild type.

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

REVISTA / JOURNAL: - J Exp Clin Cancer Res. 2013 Aug 29;32(1):59.

●● Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-59](#)

AUTORES / AUTHORS: - Wang Z; Bao Z; Yan W; You G; Wang Y; Li X; Zhang W

RESUMEN / SUMMARY: - BACKGROUND: To date, no prognostic microRNAs (miRNAs) for isocitrate dehydrogenase 1 (IDH1) wild-type glioblastoma multiformes (GBM) have been reported. The aim of the present study was to identify a miRNA signature of prognostic value for IDH1 wild-type GBM patients using miRNA expression dataset from the The Cancer Genome Atlas (TCGA). METHODS: Differential expression profiling analysis of miRNAs was performed on samples from 187 GBM patients, comprising 17 mutant-type IDH1 and 170 wild-type IDH1 samples. RESULTS: A 23-microRNA signature which was specific to the IDH1 mutation was revealed. Survival data was available for 140 of the GBM patients with wild-type IDH1. Using these data, the samples were characterized as high-risk or low-risk group according to the ranked protective scores for each of the 23 miRNAs in the 23-miRNA signature. Then, the 23 IDH1 mutation-specific miRNAs were classified as risky group and protective group miRNAs based on the significance analysis of microarrays d-score (SAM d-value) (positive value or negative value). The risky group miRNAs were found to be expressed more in the high-risk samples while the protective group miRNAs were expressed more in the low-risk samples. Patients with high protective scores had longer survival times than those with low protective scores. CONCLUSION: These findings show that IDH1 mutation-specific miRNA signature is a marker for favorable prognosis in primary GBM patients with the IDH1 wild type.

[222]

TÍTULO / TITLE: - Increased oral availability and brain accumulation of the ALK inhibitor crizotinib by coadministration of the P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Sep 7. doi: 10.1002/ijc.28475.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28475](#)

AUTORES / AUTHORS: - Tang SC; Nguyen LN; Sparidans RW; Wagenaar E; Beijnen JH; Schinkel AH

INSTITUCIÓN / INSTITUTION: - Division of Molecular Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

RESUMEN / SUMMARY: - Crizotinib is an oral tyrosine kinase inhibitor approved for treating patients with non-small cell lung cancer (NSCLC) containing an anaplastic lymphoma kinase (ALK) rearrangement. We used knockout mice to study the roles of P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) in plasma pharmacokinetics and brain accumulation of oral crizotinib, and the feasibility of improving crizotinib kinetics using coadministration of the dual ABCB1/ABCG2 inhibitor elacridar. In vitro, crizotinib was a good transport substrate of human ABCB1, but not of human ABCG2 or murine Abcg2. With low-dose oral crizotinib (5 mg/kg), Abcb1a/1b^{-/-} and Abcb1a/1b;Abcg2^{-/-} mice had an ~2-fold higher plasma AUC than wild-type mice, and a markedly (~40-fold) higher brain accumulation at 24 hr. Also at 4 hr, crizotinib brain concentrations were ~25-fold, and brain-to-plasma ratios ~14-fold higher in Abcb1a/1b^{-/-} and Abcb1a/1b;Abcg2^{-/-} mice than in wild-type mice. High-dose oral crizotinib (50 mg/kg) resulted in comparable plasma pharmacokinetics between wild-type and Abcb1a/1b^{-/-} mice, suggesting saturation of intestinal Abcb1. Nonetheless, brain accumulation at 24 hr was still ~70-fold higher in Abcb1a/1b^{-/-} than in wild-type mice. Importantly, oral elacridar coadministration increased the plasma and brain concentrations and brain-to-plasma ratios of crizotinib in wild-type mice, equaling the levels in Abcb1a/1b;Abcg2^{-/-} mice. Our results indicate that crizotinib oral availability and brain accumulation were primarily restricted by Abcb1 at a non-saturating dose, and that coadministration of elacridar with crizotinib could substantially increase crizotinib oral availability and delivery to the brain. This principle might be used to enhance therapeutic efficacy of crizotinib against brain metastases in NSCLC patients. © 2013 Wiley Periodicals, Inc.

[223]

TÍTULO / TITLE: - Clinical efficacy of second generation tyrosine kinase inhibitor and 5-azacytidine combination in chronic myelogenous leukaemia in myeloid blast crisis.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 19. pii: S0959-8049(13)00732-6. doi: 10.1016/j.ejca.2013.07.147.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejca.2013.07.147

AUTORES / AUTHORS: - Ghez D; Micol JB; Pasquier F; Auger N; Saada V; Spentchian M; Ianotto JC; Bourhis JH; Bennaceur-Griscelli A; Terre C; Castaigne S; Rigaudeau S; Rousselot P; de Botton S

INSTITUCIÓN / INSTITUTION: - Service d'Hematologie, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France.

RESUMEN / SUMMARY: - Even in the tyrosine kinase inhibitors era, the prognosis of patients with chronic myeloid leukaemia in myeloid blast crisis remains dismal with few patients surviving longer than 6months. Here we report the cases of 5 patients treated with the combination of 5-azacytidine and tyrosine kinase inhibitors for myeloid blast crisis CML. All patients achieved a complete haematological response including two with a complete cytogenetic and major molecular response. Two patients underwent an allogeneic stem cell transplantation. One died from relapse 34months from diagnosis. The second is alive and free from disease at 11months from diagnosis. The other 3 patients are still in complete haematological response after 15, 24 and 33months of follow-up. These results suggest that the combination has a significant activity in myeloid blast crisis and may increase survival.

[224]

TÍTULO / TITLE: - Clinicopathological and molecular markers associated with prognosis and treatment effectiveness of endometrial stromal sarcoma: a retrospective study in China.

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

REVISTA / JOURNAL: - Arch Gynecol Obstet. 2013 Aug 20.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00404-013-2987-5](#)

AUTORES / AUTHORS: - He L; Li JD; Xiong Y; Huang X; Huang L; Lin JX; Zhou Y; Zheng M

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, State Key Laboratory of Oncology in Southern China, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong, 510060, People's Republic of China.

RESUMEN / SUMMARY: - **PURPOSE:** To evaluate the clinicopathological and immunophenotypic characteristics of endometrial stromal sarcoma (ESS) in China. **METHODS AND MATERIALS:** Seventy-two consecutive ESS cases treated between 1995 and 2009 were retrospectively reviewed. **RESULTS:** Sixty-three patients received surgical treatment. Forty-one patients underwent pelvic lymphadenectomy. In paraffin-embedded specimens, expression of the following molecular markers was detected: CD10 (27/36), vimentin (37/38), HHF35 (3/32), S-100 (0/25), desmin (2/29), CD117 (0/23), CD34 (2/24), alpha-inhibin (0/17), CK (1/34), CD99 (4/9), smooth muscle actin (5/25), EMA (0/7), estrogen receptor (13/16) and progesterone receptor (13/16). CD10 and vimentin were expressed more frequently in these specimens. Tumor classification, CD10 and surgical procedures were significantly associated with disease-free survival (DFS). Surgical procedures were significantly associated with overall survival (OS). Tumor stage (P = 0.024) and surgical procedure (P = 0.042) were found to be significant independent prognostic factors for DFS. No complete or partial response was observed among patients who received radiotherapy or chemotherapy. **CONCLUSIONS:** Our results indicate that total hysterectomy with bilateral salpingo-oophorectomy followed by pelvic lymphadenectomy is associated with an improved

treatment outcome. CD10-negative expression may contribute to the malignant characteristics and recurrence associated with ESS.

[225]

TÍTULO / TITLE: - Predictive biomarkers for cancer therapy with PARP inhibitors.

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

REVISTA / JOURNAL: - Oncogene. 2013 Sep 16. doi: 10.1038/onc.2013.352.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.352](#)

AUTORES / AUTHORS: - Michels J; Vitale I; Saporbaev M; Castedo M; Kroemer G

INSTITUCIÓN / INSTITUTION: - [1] INSERM, U848, Villejuif, France [2] Institut Gustave Roussy, Villejuif, France [3] Université de Paris Sud, Villejuif, France.

RESUMEN / SUMMARY: - Poly(ADP-ribose) polymerase (PARP) inhibitors have raised high expectations for the treatment of multiple malignancies. PARP inhibitors, which can be used as monotherapies or in combination with DNA-damaging agents, are particularly efficient against tumors with defects in DNA repair mechanisms, in particular the homologous recombination pathway, for instance due to BRCA mutations. Thus, deficient DNA repair provides a framework for the success of PARP inhibitors in medical oncology. Here, we review encouraging results obtained in recent clinical trials investigating the safety and efficacy of PARP inhibitors as anticancer agents. We discuss emerging mechanisms of regulation of homologous recombination and how inhibition of DNA repair might be used in cancer therapy. We surmise that the identification of patients that are likely to benefit from PARP inhibition will improve the clinical use of PARP inhibitors in a defined target population. Thus, we will place special emphasis on biomarker discovery. Oncogene advance online publication, 16 September 2013; doi:10.1038/onc.2013.352.

[226]

TÍTULO / TITLE: - Phase II study of pemetrexed plus intermittent erlotinib combination therapy for pretreated advanced non-squamous non-small cell lung cancer with documentation of epidermal growth factor receptor mutation status.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Aug 6. pii: S0169-5002(13)00331-0. doi: 10.1016/j.lungcan.2013.07.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.lungcan.2013.07.022](#)

AUTORES / AUTHORS: - Minami S; Kijima T; Hamaguchi M; Nakatani T; Koba T; Takahashi R; Takeuchi Y; Kida H; Nagatomo I; Yamamoto S; Tachibana I; Komuta K; Kawase I

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Osaka Police Hospital, 10-31 Kitayama-cho, Tennoji-ku, Osaka 543-0035, Japan.

RESUMEN / SUMMARY: - INTRODUCTION: Erlotinib and pemetrexed have been approved for the second-line and maintenance treatment of non-small cell lung cancer (NSCLC). With the recommended doses determined by our previous phase I study, we conducted a phase II study to evaluate the efficacy and safety of combination of the two agents in pretreated non-squamous NSCLC patients. METHODS: This study was performed in patients with stage IIIB/IV or post-surgically recurrent non-squamous NSCLC whose disease had progressed on or after receiving first-line chemotherapy. Patients received 500mg/m² of intravenous pemetrexed every 21 days and 150mg of oral erlotinib on days 2-16 until disease progression, unacceptable toxicity, or withdrawal of consent. The expected response rate and threshold were defined as 33.5% and 10%, respectively. Assuming a one-sided alpha of 5%, a power of 80%, the possible deviation from assessment, 26 patients were necessary. RESULTS: A total of 27 patients, 16 males and 11 females were recruited. Patients had the median age of 70 years (range, 48-80 years) and included 21 stage IV diseases, 22 adenocarcinomas. Epidermal growth factor receptor (EGFR) mutations were examined in all patients. One patient had positive EGFR mutation, but the other 26 patients had wild-type EGFR. The median number of treatment courses was 3 (range, 1 to over 19). The best overall response rate and disease control rate were 11.1% and 63.0%, respectively. The median progression-free survival and overall survival were 2.8 months (95% confidence interval (CI); 1.9-7.5 months) and 15.8 months (95% CI; 9.3 months to not available), respectively. Dermal, hepatic, gastrointestinal and hematological disorders were the frequently observed adverse events. One patient experienced grade 3 drug-induced interstitial lung disease. CONCLUSIONS: We could not demonstrate the add-on effect of intermittent erlotinib on pemetrexed in a second-line setting for patients with non-squamous NSCLC without EGFR mutations.

[227]

TÍTULO / TITLE: - mTOR inhibitor associated noninfectious pneumonitis in patients with renal cell cancer: management, predictors, and outcomes.

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

REVISTA / JOURNAL: - BJU Int. 2013 Aug 23. doi: 10.1111/bju.12420.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12420](#)

AUTORES / AUTHORS: - Atkinson BJ; Cauley DH; Ng C; Millikan RE; Xiao L; Corn P; Jonasch E; Tannir NM

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy Clinical Programs University of Texas MD Anderson Cancer Center, Houston, TX.

RESUMEN / SUMMARY: - OBJECTIVE: To characterize the incidence, onset, management, predictors, and clinical impact of mTOR inhibitor associated noninfectious pneumonitis (NIP) on patients with metastatic renal cell carcinoma. PATIENTS AND METHODS: Retrospective review of 310 patients with metastatic renal cell carcinoma who

received temsirolimus and/or everolimus between 6/1/2007 and 10/1/2010. Clinical correlations were made with serial radiologic imaging. Fisher's exact, Wilcoxon rank sum, and logistic regression analysis were performed to evaluate the association of NIP with demographic or clinical factors. Log rank and Cox proportional hazards regression analysis were used for the time-to-event analysis. RESULTS: NIP occurred in 6% of temsirolimus and 23% of everolimus treated patients. Symptoms included cough, dyspnea, and fever (median of two and three symptoms per patient, respectively). Median NCI-CTCAE pneumonitis grade was 2 for both groups. Older age and everolimus treatment were predictive of NIP. Patients who developed NIP had significantly longer time on treatment (median 4.1 months vs 2 months) and overall survival (OS) (median 15.4 months vs 7.4 months). NIP was a predictor of improved OS by multivariate analysis. CONCLUSIONS: An increased incidence of NIP was observed in everolimus treated patients. Improved OS in patients who developed NIP is an intriguing finding and should be further investigated. Given the incidence, morbidity, and outcomes seen in patients on everolimus who develop NIP, management should include proactive monitoring and treatment of NIP with the goal of preserving mTOR inhibitor therapy.

[228]

TÍTULO / TITLE: - Induction of apoptosis in human myeloid leukemia cells by remote exposure of resistive barrier plasma.

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

REVISTA / JOURNAL: - Biotechnol Bioeng. 2013 Sep 10. doi: 10.1002/bit.25114.

●● Enlace al texto completo (gratis o de pago) [1002/bit.25114](#)

AUTORES / AUTHORS: - Thiyagarajan M; Anderson H; Gonzales XF

INSTITUCIÓN / INSTITUTION: - Plasma Engineering Research Lab (PERL), Texas A&M University - Corpus Christi, 6300 Ocean Drive, Unit 5797, Corpus Christi, Texas, 78412.

RESUMEN / SUMMARY: - Cold atmospheric plasma (CAP), an ambient temperature ionized gas, is gaining extensive interest as a promising addition to anti-tumor therapy primarily due to the ability to generate and control delivery of electrons, ions, excited molecules, UV photons, and reactive species such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) to a specific site. The heterogeneous composition of CAP offers the opportunity to mediate several signaling pathways that regulate tumor cells. Consequently, the array of CAP generated products has limited the identification of the mechanisms of action on tumor cells. The aim of this work is to assess the cell death response of human myeloid leukemia cells by remote exposure to CAP generated RNS by utilizing a novel resistive barrier discharge system that primarily produces RNS. The effect of variable treatments of CAP generated RNS was tested in THP-1 cell (human monocytic leukemia cell line), a model for haematological malignancy. The number of viable cells was evaluated with erythrosine-B staining,

while apoptosis and necrosis was assessed by endonuclease cleavage observed by agarose gel electrophoresis and detection of cells with the exclusionary dye propidium iodide and fluorescently labeled annexin-V by flow cytometry and fluorescent microscopy. Our observations indicate that treatment dosage levels of 45 seconds of exposure to CAP emitted RNS induced apoptotic cell death and for higher dosage conditions of ≥ 50 seconds of exposure to CAP induced necrosis. Overall the results suggest that CAP emitted RNS play a significant role in the anti-tumor potential of CAP. Biotechnol. Bioeng. © 2013 Wiley Periodicals, Inc.

[229]

TÍTULO / TITLE: - Sulfotransferase genetic variation: from cancer risk to treatment response.

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

REVISTA / JOURNAL: - Drug Metab Rev. 2013 Sep 6.

●● Enlace al texto completo (gratis o de pago) [3109/03602532.2013.835621](#)

AUTORES / AUTHORS: - Daniels J; Kadlubar S

INSTITUCIÓN / INSTITUTION: - Department of Medical Genetics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

RESUMEN / SUMMARY: - Abstract Cytosolic sulfotransferases (SULTs) are phase II detoxification enzymes that are involved in the biotransformation of a wide variety of structurally diverse endo- and xenobiotics. Single-nucleotide polymorphisms (SNPs) in SULTs can alter the phenotype of the translated proteins. SNPs in some SULTs are fairly uncommon in the population, but some, most notably for SULT isoform 1^a1, are commonly found and have been associated with cancer risk for a variety of tumor sites and also with response to therapeutic agents. SNPs in many SULTs vary by ethnicity, another factor that could influence SULT-associated disease risk and pharmacogenetics. This review surveys the current knowledge of SULT genetic variability in relation to cancer risk and response to therapy, focusing primarily on SULT1A1.

TÍTULO / TITLE: - Quantification of serum hepatitis B surface antigen in predicting the response of pegylated interferon alfa-2^a in HBeAg-positive chronic hepatitis B with prior lamivudine exposure.

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

REVISTA / JOURNAL: - Virol J. 2013 Sep 6;10(1):277.

●● Enlace al texto completo (gratis o de pago) [1186/1743-422X-10-277](#)

AUTORES / AUTHORS: - Weng M; Zeng WZ; Wu XL; Zhang Y; Jiang MD; Wang Z; Zhou DJ; He X

RESUMEN / SUMMARY: - AIMS: Majority of previous studies of pegylated interferon alpha-2^a (PegIFNalpha-2^a) forced on naive chronic hepatitis B (CHB) patients, and the data of PegIFNalpha-2^a in therapy of patients with prior exposure to nucleos(t)ide analogues is rare. This study aimed to investigate the predictive role of serum quantitative hepatitis B surface antigen (HBsAg) in predicting sustained response of PegIFNalpha-2^a in HBeAg-positive CHB patients with prior lamivudine exposure. **METHODS:** Forty-six patients with prior lamivudine exposure received PegIFNalpha-2^a for 12 months and followed-up for 6 months. The clinical features of responders and non-responders were compared, and the predictive role of quantitative HBsAg in predicting responders at the end of follow-up was evaluated. Responders were defined as an ALT normalization, HBeAg seroconversion and sustained virological response at the end of follow-up. **RESULTS:** In this cohort, only 26.1% (12/46) patients were responders. The baseline characteristics of the responders and non-responders were similar; however, the rates of ALT normalization, HBV DNA undetectability and HBeAg seroconversion were all significantly higher in responders than that in non-responders. During the treatment and follow-up, the HBsAg levels were all significantly lower in responders than that in non-responders. In predicting responders, the serum HBsAg cutoff of 6000 IU/mL at months 6 had a positive predictive value of 73.3 and a negative predictive value of 96.8%, and with an area under the receiver operating characteristic curve of 0.869. **CONCLUSION:** The responders toward PegIFNalpha-2^a in CHB patients with prior lamivudine exposure is not high, and serum HBsAg <6000 IU/ML at months 6 of on-treatment had a high value to predict long-term outcomes of treatment.

[230]

TÍTULO / TITLE: - RAF Inhibition Overcomes Resistance to TRAIL-Induced Apoptosis in Melanoma Cells.

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

REVISTA / JOURNAL: - J Invest Dermatol. 2013 Aug 16. doi: 10.1038/jid.2013.347.

●● Enlace al texto completo (gratis o de pago) [1038/jid.2013.347](#)

AUTORES / AUTHORS: - Berger A; Quast SA; Plotz M; Kuhn NF; Trefzer U; Eberle J

INSTITUCIÓN / INSTITUTION: - Department of Dermatology and Allergy, Skin Cancer Center, University Medical Center Charite, Berlin, Germany.

RESUMEN / SUMMARY: - Mutated BRAF represents a critical oncogene in melanoma, and selective inhibitors have been approved for melanoma therapy. However, the molecular consequences of RAF inhibition in melanoma cells remained largely elusive. Here, we investigated the effects of the pan-RAF inhibitor L-779,450, which inhibited cell proliferation both in BRAF-mutated and wild-type melanoma cell lines. It furthermore enhanced apoptosis in combination with the death ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and overcame TRAIL resistance in melanoma cells. Enhanced apoptosis coincided with activation of mitochondrial pathways, seen by loss of mitochondrial membrane potential and release of

cytochrome c, Smac (second mitochondria-derived activator of caspases), and apoptosis-inducing factor (AIF). Subsequently, caspase-9 and -3 were activated. Apoptosis induction by L-779,450/TRAIL was prevented by Bcl-2 overexpression and was dependent on Bax. Thus, activation of Bax by L-779,450 alone was demonstrated by Bax conformational changes, whereas Bak was not activated. Furthermore, the BH3-only protein Bim was upregulated in response to L-779,450. The significant roles of Smac, Bax, and Bim in this setting were proven by small interfering RNA (siRNA)-mediated knockdown experiments. L-779,450 also resulted in morphological changes indicating autophagy confirmed by the autophagy marker light chain 3-II (LC3-II). The pro-apoptotic effects of L-779,450 may explain the antitumor effects of RAF inhibition and may be considered when evaluating RAF inhibitors for melanoma therapy. *Journal of Investigative Dermatology* advance online publication, 19 September 2013; doi:10.1038/jid.2013.347.

[231]

TÍTULO / TITLE: - Knockdown of dual specificity phosphatase 4 enhances the chemosensitivity of MCF-7 and MCF-7/ADR breast cancer cells to doxorubicin.

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

REVISTA / JOURNAL: - *Exp Cell Res.* 2013 Sep 3. pii: S0014-4827(13)00366-2. doi: 10.1016/j.yexcr.2013.08.023.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexcr.2013.08.023](#)

AUTORES / AUTHORS: - Liu Y; Du F; Chen W; Yao M; Lv K; Fu P

INSTITUCIÓN / INSTITUTION: - Department of Breast Surgery Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China.

RESUMEN / SUMMARY: - **BACKGROUND:** Breast cancer is the major cause of cancer-related deaths in females world-wide. Doxorubicin-based therapy has limited efficacy in breast cancer due to drug resistance, which has been shown to be associated with the epithelial-to-mesenchymal transition (EMT). However, the molecular mechanisms linking the EMT and drug resistance in breast cancer cells remain unclear. Dual specificity phosphatase 4 (DUSP4), a member of the dual specificity phosphatase family, is associated with cellular proliferation and differentiation; however, its role in breast cancer progression is controversial. **METHODS:** We used cell viability assays, Western blotting and immunofluorescent staining, combined with siRNA interference, to evaluate chemoresistance and the EMT in MCF-7 and adriamycin-resistant MCF-7/ADR breast cancer cells, and investigate the underlying mechanisms. **RESULTS:** Knockdown of DUSP4 significantly increased the chemosensitivity of MCF-7 and MCF-7/ADR breast cancer cells to doxorubicin, and MCF-7/ADR cells which expressed high levels of DUSP4 had a mesenchymal phenotype. Furthermore, knockdown of DUSP4 reversed the EMT in MCF-7/ADR cells, as demonstrated by upregulation of epithelial

biomarkers and downregulation of mesenchymal biomarkers, and also increased the chemosensitivity of MCF-7/ADR cells to doxorubicin. CONCLUSIONS: DUSP4 might represent a potential drug target for inhibiting drug resistance and regulating the process of the EMT during the treatment of breast cancer.

[232]

TÍTULO / TITLE: - Efficacy of estramustine phosphate sodium hydrate (EMP) monotherapy in castration-resistant prostate cancer patients: report of 102 cases and review of literature.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):717. doi: 10.1007/s12032-013-0717-2. Epub 2013 Sep 5.

●● Enlace al texto completo (gratuito o de pago) [1007/s12032-013-0717-2](#)

AUTORES / AUTHORS: - Matsumoto K; Tanaka N; Hayakawa N; Ezaki T; Suzuki K; Maeda T; Ninomiya A; Nakamura S

INSTITUCIÓN / INSTITUTION: - Department of Urology, Tokyo Saiseikai Central Hospital, Mita 1-4-17, Minato-ku, Tokyo, 108-0073, Japan, kazz_matsumoto@yahoo.co.jp.

RESUMEN / SUMMARY: - This retrospective chart review study was conducted to evaluate the efficacy of estramustine phosphate sodium hydrate (EMP) monotherapy in patients with castration-resistant prostate cancer (CRPC) and to determine who would benefit from EMP therapy. EMP was administered at a daily dose of 560 mg to 102 patients as a third-line therapy, who had already received combined androgen blockade (CAB) and subsequent alternative antiandrogen therapy. The responses to EMP after its induction and its toxicity were evaluated. We also analyzed the association between the clinicopathological factors of the patients and their responses to EMP therapy. A reduction in the serum prostate-specific antigen (PSA) 4 weeks after induction was observed in 70 patients (68.6 %), while 30 cases (29.4 %) achieved more than 50 % reduction of PSA. Long-term reduction of PSA from baseline for more than 6 months was observed in 31 patients (30.4 %). EMP treatment was discontinued in 11 patients (10.8 %) because of side effects (nausea in six patients, gynecomastia in three patients, eruption in one patient, and liver dysfunction in one patient). Multivariate analysis demonstrated that long duration of prior hormonal therapy was an independent favorable factor for reduced PSA levels, long responses, and overall survival. The data suggest that oral EMP administration as a third-line monotherapy is well tolerated and effective to some degree in patients with CRPC who have already received CAB and subsequent alternative antiandrogen therapy. Thus, EMP can be regarded as one treatment option, especially for patients whose prior duration of hormonal therapy was long.

[233]

TÍTULO / TITLE: - Prediction of tamoxifen outcome by genetic variation of CYP2D6 in postmenopausal women with early breast cancer.

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

REVISTA / JOURNAL: - Br J Clin Pharmacol. 2013 Aug 22. doi: 10.1111/bcp.12229.

●● Enlace al texto completo (gratis o de pago) [1111/bcp.12229](#)

AUTORES / AUTHORS: - Brauch H; Schwab M

INSTITUCIÓN / INSTITUTION: - Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University Tuebingen, Germany.

RESUMEN / SUMMARY: - The question of whether genetic polymorphisms of CYP2D6 can affect treatment outcome in patients with early postmenopausal estrogen receptor (ER)-positive breast cancer has been a matter of debate over the past few years. In this article we revisit the hypothesis of CYP2D6 being a potential tamoxifen outcome predictor and provide detailed insight into the ongoing controversy that prevented the CYP2D6 marker from being accepted by the scientific and clinical community. We summarize the available pharmacokinetic, pharmacodynamic and pharmacogenetic evidence and resolve the controversy based on the recognized methodological and statistical issues. The cumulative evidence suggests that genotyping for CYP2D6 is clinically relevant in postmenopausal women. This is important, because the clarification of this issue has the potential to resolve a clinical management question that is relevant to hundreds of thousands of women diagnosed with ER-positive breast cancer each year, who should not be denied effective endocrine therapy.

[234]

TÍTULO / TITLE: - Digitoxin sensitizes glioma cells to TRAIL-mediated apoptosis by upregulation of death receptor 5 and downregulation of survivin.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Sep 16.

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

[1097/CAD.0000000000000015](#)

AUTORES / AUTHORS: - Lee DH; Lee CS; Kim DW; Ae JE; Lee TH

INSTITUCIÓN / INSTITUTION: - aDepartment of Neurosurgery, School of Medicine
bDepartment of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, Virginia, USA
cDepartment of Obstetrics and Gynecology, College of Medicine, Kosin University, Korea.

RESUMEN / SUMMARY: - Glioblastoma multiforme is the most lethal and aggressive astrocytoma among primary brain tumors in adults. However, most glioblastoma cells have been reported to be resistant to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. Here, we have shown that digitoxin (DT), a clinically approved cardiac glycoside for heart failure, can induce TRAIL-mediated apoptosis of

glioblastoma cells. DT in noncytotoxic doses (20 nmol/l) can increase TRAIL-induced apoptosis in TRAIL-resistant U87MG glioblastoma cells. Treatment with DT led to apoptosis and a robust reduction in the levels of the antiapoptotic protein survivin by inducing its proteasomal degradation; however, it did not affect the levels of many other apoptosis regulators. Moreover, silencing survivin with small interfering RNAs sensitized glioma cells to TRAIL-induced apoptosis, underscoring the functional role of survivin depletion in the TRAIL-sensitizing actions of DT. We demonstrate that inactivation of survivin and death receptor 5 expression by DT is sufficient to restore TRAIL sensitivity in resistant glioma cells. Our results suggest that combining DT with TRAIL treatments may be useful in the treatment of TRAIL-resistant glioma cells.

[235]

TÍTULO / TITLE: - The predictive value of semaphorins 3 expression in biopsies for biochemical recurrence of patients with low- and intermediate-risk prostate cancer.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(6):683-9. doi: 10.4149/neo_2013_087.

●● [Enlace al texto completo \(gratis o de pago\) 4149/neo_2013_087](#)

AUTORES / AUTHORS: - Li K; Chen MK; Li LY; Lu MH; Shao ChK; Su ZL; He D; Pang J; Gao X

RESUMEN / SUMMARY: - The class-3 semaphorins (Sema3A-F, Sema3s) are initially identified to play an important role in axonal guidance and cell migration. Our previous studies showed that Sema3s are also involved in the lymph node metastasis of prostate cancer, and are likely to modulate the behavior of prostate cancer with pro-tumoral or an anti-tumoral effect, depending on their subtypes. However, no study has critically investigated the value of Sema3s expression in preoperative biopsy samples for the prediction of biochemical recurrence (BCR) after radical prostatectomy. In this study, we evaluated Sema3s expression by immunohistochemistry on 198 prostate biopsies with low- and intermediate-risk localized prostate cancer. The median follow-up was 42 months (range, 6-60) for all patients. Our results showed that Sema3A (OR: 0.19, P<0.001), Sema3B (OR: 0.38, P=0.003), Sema3E (OR: 0.39, P=0.007), and Sema3C (OR: 2.31, P=0.014) staining were independent predictors of BCR on multivariable analysis. Sema3A, 3B, 3C and 3E expression demonstrated potential values in predicting BCR upon survival analysis (P=0.001, P=0.003, P=0.029, P=0.037, respectively, Log-rank test). Our findings suggested that Sema3A, 3B, 3C, and 3E immunostaining in prostate biopsies, as supplements to clinicopathological parameters, could be used for predicting BCR in low- and intermediate-risk prostate cancer patients after radical prostatectomy. Specially, concurrent Sema3C-positive and Sema3A-negative, 3B-negative, 3E-negative staining is associated with an adverse prognosis. Further prospective studies in larger patient populations are needed to validate the current observations. Keywords: biochemical recurrence, biopsy, class-3 semaphorins, immunohistochemistry, prostate cancer, radical prostatectomy.

[236]

TÍTULO / TITLE: - Novel Quinic Acid Derivative KZ-41 Prevents Retinal Endothelial Cell Apoptosis Without Inhibiting Retinoblastoma Cell Death Through p38 Signaling.

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

REVISTA / JOURNAL: - Invest Ophthalmol Vis Sci. 2013 Sep 3;54(9):5937-43. doi: 10.1167/iovs.13-12326.

●● Enlace al texto completo (gratis o de pago) [1167/iovs.13-12326](#)

AUTORES / AUTHORS: - Zhang Q; Jiang Y; Toutouchian J; Wilson MW; Morales-Tirado V; Miller DD; Yates CR; Steinle JJ

INSTITUCIÓN / INSTITUTION: - Department of Ophthalmology, University of Tennessee Health Science Center, Memphis, Tennessee.

RESUMEN / SUMMARY: - PURPOSE: To determine whether a novel NF-kappaB inhibitor, KZ-41, can inhibit melphalan's actions on retinal endothelial cell (REC) inflammation and apoptosis, without eliminating the chemotherapeutic efficacy of melphalan on cell death of retinoblastoma cells (Y79). METHODS: RECs were cultured in M131 medium supplemented with growth factors and antibiotics. Once cells reached confluence, they were treated with or without 10 muM KZ-41, following treatment with 4 mug/mL melphalan. Cell proteins were extracted and analyzed for intracellular adhesion molecule 1 (ICAM-1) levels and Cell Death ELISA. RECs were also transfected with or without NF-kappaB siRNA or treated with SB202190 (p38 [mitogen activated protein kinase] MAPK inhibitor) before melphalan treatment to determine the involvement of NF-kappaB and p38 MAPK in REC apoptosis and ICAM-1 levels. We also cultured retinoblastoma cells (Y79) in RPMI-1640 medium supplemented with 20% fetal bovine serum and performed a Cell Death ELISA after melphalan + KZ-41 treatment to determine if the treatments altered melphalan's ability to promote cell death of Y79 cells. RESULTS: KZ-41 inhibited melphalan-stimulation of ICAM-1 levels and REC apoptosis, whereas KZ-41 did not alter melphalan's effects on Y79 cells. KZ-41's protective effects on REC were mediated through p38 MAPK activation. Although KZ-41 blocked both NF-kappaB- and p38 MAPK-dependent ICAM-1 stimulation; the p38 MAPK/ICAM-1 pathway appears to be the primary pathway involved in melphalan-induced REC apoptosis. CONCLUSIONS: KZ-41 protects REC against melphalan-induced upregulation of ICAM-1 and apoptosis through p38 MAPK-dependent pathways.

[237]

TÍTULO / TITLE: - Lamin A/C cleavage by caspase-6 activation is crucial for apoptotic induction by photodynamic therapy with hexaminolevulinate in human B-cell lymphoma cells.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Oct 1;339(1):25-32. doi: 10.1016/j.canlet.2013.07.026. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.07.026](https://doi.org/10.1016/j.canlet.2013.07.026)

AUTORES / AUTHORS: - Shahzidi S; Brech A; Sioud M; Li X; Suo Z; Nesland JM; Peng Q

INSTITUCIÓN / INSTITUTION: - Department of Pathology, The Norwegian Radium Hospital, Oslo University Hospital and Medical Faculty, University of Oslo, Oslo, Norway.

RESUMEN / SUMMARY: - Photodynamic therapy (PDT) with a light-activated drug is an approved modality for cancer treatment. Hexaminolevulinate (HAL), a hexylester of 5-aminolevulinic acid as the photosensitising protoporphyrin IX (PpIX) precursor, is clinically used for both PDT and photodetection. Our previous studies have shown that HAL-PDT can effectively induce apoptosis in several human blood malignant cell lines. However, the mechanisms involved in the apoptotic induction are still not fully elucidated. In this study we have focused on the role of cellular lamin A/C in the apoptotic induction. HAL-PDT-mediated apoptosis was confirmed by various techniques including fluorescence microscopy and electron microscopy in both human B-cell lymphoma Ramos and Daudi cell lines. The lamin A/C, together with caspases-6 and -3, was cleaved during the apoptosis. Western blots, immunocytochemistry, fluorescence microscopy and electron microscopy demonstrated that the specific caspase-6inhibitor abrogated the HAL-PDT-mediated cleavages of both caspase-6 and lamin A/C and subsequent apoptosis in these two cell lines, suggesting that the cleavage of lamin A/C by the caspase-6 activation is crucial for such apoptotic induction.

[238]

TÍTULO / TITLE: - The pan-Bcl-2 blocker obatoclax promotes the expression of Puma, Noxa, and Bim mRNA and induces apoptosis in neoplastic mast cells.

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

REVISTA / JOURNAL: - J Leukoc Biol. 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1189/jlb.1112609](https://doi.org/10.1189/jlb.1112609)

AUTORES / AUTHORS: - Peter B; Cerny-Reiterer S; Hadzijusufovic E; Schuch K; Stefanzl G; Eisenwort G; Gleixner KV; Hoermann G; Mayerhofer M; Kundi M; Baumgartner S; Sperr WR; Pickl WF; Willmann M; Valent P

INSTITUCIÓN / INSTITUTION: - *Ludwig-Boltzmann Cluster Oncology, double daggerDepartment of Internal Medicine I, Division of Hematology and Hemostaseology, Institutes of section signImmunology and #Environmental Health, Center for Public Health, and Departments of parallelLaboratory Medicine and **Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria;

RESUMEN / SUMMARY: - Advanced SM is an incurable neoplasm with short survival time. So far, no effective therapy is available for these patients. We and others have shown recently that neoplastic MC in ASM and MCL express antiapoptotic Mcl-1, Bcl-2, and

Bcl-xL. In this study, we examined the effects of the pan-Bcl-2 family blocker obatoclax (GX015-070) on primary neoplastic MC, the human MC leukemia cell line HMC-1, and the canine mastocytoma cell line C2. Obatoclax was found to inhibit proliferation in primary human neoplastic MC (IC50: 0.057 μ M), in HMC-1.2 cells expressing KIT D816V (IC50: 0.72 μ M), and in HMC-1.1 cells lacking KIT D816V (IC50: 0.09 μ M), as well as in C2 cells (IC50: 0.74 μ M). The growth-inhibitory effects of obatoclax in HMC-1 cells were accompanied by an increase in expression of Puma, Noxa, and Bim mRNA, as well as by apoptosis, as evidenced by microscopy, TUNEL assay, and caspase cleavage. Viral-mediated overexpression of Mcl-1, Bcl-xL, or Bcl-2 in HMC-1 cells was found to introduce partial resistance against apoptosis-inducing effects of obatoclax. We were also able to show that obatoclax synergizes with several other antineoplastic drugs, including dasatinib, midostaurin, and bortezomib, in producing apoptosis and/or growth arrest in neoplastic MC. Together, obatoclax exerts major growth-inhibitory effects on neoplastic MC and potentiates the antineoplastic activity of other targeted drugs. Whether these drug effects can be translated to application in patients with advanced SM remains to be determined.

[239]

TÍTULO / TITLE: - RASSF6 tumor suppressor regulates apoptosis and cell cycle via MDM2 and p53.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.507384](https://doi.org/10.1074/jbc.M113.507384)

AUTORES / AUTHORS: - Iwasa H; Kudo T; Maimaiti S; Ikeda M; Maruyama J; Nakagawa K; Hata Y

INSTITUCIÓN / INSTITUTION: - Tokyo Medical and Dental University, Japan.

RESUMEN / SUMMARY: - Ras-association domain family (RASSF) 6 is a member of the C-terminal RASSF proteins like RASSF1A and RASSF3. RASSF6 is involved in apoptosis in various cells under miscellaneous conditions, but it remains to be clarified how RASSF6 exerts tumor suppressive roles. We previously reported that RASSF3 facilitates the degradation of MDM2, a major E3 ligase of p53, and stabilizes p53 to function as a tumor suppressor. In this study, we demonstrate that RASSF6 overexpression induces G1/S arrest in p53-positive cells. Its depletion prevents ultraviolet (UV)- and VP-16-induced apoptosis and the G1/S arrest in HCT116 and U2OS cells. RASSF6-induced apoptosis partially depends on p53. RASSF6 binds MDM2 and facilitates its ubiquitination. RASSF6 depletion blocks the increase of p53 in response to UV exposure and the up-regulation of p53 target genes. RASSF6 depletion delays DNA repair in UV- and VP-16-treated cells and increases polyploid cells after VP-16 treatment. These findings indicate that RASSF6 stabilizes p53, regulates apoptosis and cell cycle, and functions as a tumor suppressor. Together with the previous reports

about RASSF1A and RASSF3, the stabilization of p53 may be the common function of the C-terminal RASSF proteins.

[240]

TÍTULO / TITLE: - Structural Basis and Targeting of the Interaction between Fibroblast Growth Factor-Inducible 14 and Tumor Necrosis Factor-like Weak Inducer of Apoptosis.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.493536](https://pubs.biochem.org/doi/10.1074/jbc.M113.493536)

AUTORES / AUTHORS: - Dhruv H; Loftus JC; Narang P; Petit JL; Fameree M; Burton J; Tchegho G; Chow D; Yin H; Al-Abed Y; Berens ME; Tran NL; Meurice N

INSTITUCIÓN / INSTITUTION: - The Translational Genomics Research Institute, United States;

RESUMEN / SUMMARY: - Deregulation of the TWEAK-Fn14 signaling pathway is observed in many diseases including inflammation, autoimmune diseases, and cancer. Activation of Fn14 signaling by TWEAK binding triggers cell invasion and survival and therefore represents an attractive pathway for therapeutic intervention. Based on structural studies of the TWEAK-binding cysteine rich domain of Fn14, several homology models of TWEAK were built to investigate plausible modes of TWEAK-Fn14 interaction. Two promising models, centered on different anchoring residues of TWEAK [Tyrosine 176 (Y176) and Tryptophan 231 (W231)], were prioritized using a data-driven strategy. Site-directed mutagenesis of TWEAK at Y176, but not W231, resulted in the loss of TWEAK binding to Fn14 substantiating Y176 as the anchoring residue. Importantly, mutation of TWEAK at Y176 did not disrupt TWEAK trimerization, but failed to induce Fn14 mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) signaling. The validated structural models were utilized in a virtual screen to design a targeted library of small molecules predicted to disrupt the TWEAK-Fn14 interaction. 129 small molecules were screened iteratively, with identification of molecules producing up to 37% inhibition of TWEAK-Fn14 binding. In summary, we present a data-driven in silico study revealing key structural elements of the TWEAK-Fn14 interaction, followed by experimental validation, serving as a guide for the design of small molecule inhibitors of the TWEAK-Fn14 ligand-receptor interaction. Our results validate the TWEAK-Fn14 interaction as a chemically tractable target and provide the foundation for further exploration utilizing chemical biology approaches focusing on validating this system as a therapeutic target in invasive cancers.

[241]

TÍTULO / TITLE: - c-Myc and Her2 cooperate to drive a stem-like phenotype with poor prognosis in breast cancer.

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

REVISTA / JOURNAL: - Oncogene. 2013 Sep 23. doi: 10.1038/onc.2013.368.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.368](#)

AUTORES / AUTHORS: - Nair R; Roden DL; Teo WS; McFarland A; Junankar S; Ye S; Nguyen A; Yang J; Nikolic I; Hui M; Morey A; Shah J; Pfefferle AD; Usary J; Selinger C; Baker LA; Armstrong N; Cowley MJ; Naylor MJ; Ormandy CJ; Lakhani SR; Herschkowitz JI; Perou CM; Kaplan W; O'Toole SA; Swarbrick A

INSTITUCIÓN / INSTITUTION: - Cancer Research Division, The Kinghorn Cancer Centre and Cancer Research Program Garvan Institute of Medical Research, Darlinghurst, NSW, Australia.

RESUMEN / SUMMARY: - The HER2 (ERBB2) and MYC genes are commonly amplified in breast cancer, yet little is known about their molecular and clinical interaction. Using a novel chimeric mammary transgenic approach and in vitro models, we demonstrate markedly increased self-renewal and tumour-propagating capability of cells transformed with Her2 and c-Myc. Coexpression of both oncoproteins in cultured cells led to the activation of a c-Myc transcriptional signature and acquisition of a self-renewing phenotype independent of an epithelial-mesenchymal transition programme or regulation of conventional cancer stem cell markers. Instead, Her2 and c-Myc cooperated to induce the expression of lipoprotein lipase, which was required for proliferation and self-renewal in vitro. HER2 and MYC were frequently coamplified in breast cancer, associated with aggressive clinical behaviour and poor outcome. Lastly, we show that in HER2+ breast cancer patients receiving adjuvant chemotherapy (but not targeted anti-Her2 therapy), MYC amplification is associated with a poor outcome. These findings demonstrate the importance of molecular and cellular context in oncogenic transformation and acquisition of a malignant stem-like phenotype and have diagnostic and therapeutic consequences for the clinical management of HER2+ breast cancer. Oncogene advance online publication, 23 September 2013; doi:10.1038/onc.2013.368.

[242]

TÍTULO / TITLE: - Triticuside A, a dietary flavonoid, inhibits proliferation of human breast cancer cells via inducing apoptosis.

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

REVISTA / JOURNAL: - Nutr Cancer. 2013;65(6):891-9. doi: 10.1080/01635581.2013.802001.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.802001](#)

AUTORES / AUTHORS: - Shan Y; Zhang Y; Guan FQ; Sun H; Ren XC; Chen Y; Feng X; Yang JM

RESUMEN / SUMMARY: - In this study we demonstrated that Triticuside A, one of the flavonoid compounds isolated from wheat bran, induced apoptosis and inhibited proliferation of human breast cancer cells. Triticuside A inhibited the proliferation of human breast cancer cells (MCF-7 and MDA-MB-231) in a dose-dependent manner but barely showed cytotoxicity to the normal human fibroblasts. Triticuside A-induced apoptosis was accompanied by a significant decrease of Mcl-1 and Bcl-2 proteins and by an increase of cleavage of caspases-3, -7, -9, and PARP. Triticuside A also suppressed the level of phospho-Akt and its downstream targets, mTOR and P70 S6 kinase. LY294002, a specific inhibitor of PI3K, significantly enhanced the Triticuside A-induced apoptosis. Moreover LY294002 not only downregulated the level of phospho-Akt but also enhanced the inhibition of Mcl-1 expression when combined with Triticuside A. Our results demonstrate for the first time the specific apoptogenic activity of Triticuside A in tumor cells and involvement of the mitochondrial apoptosis pathway and Akt/mTOR signaling pathway. Thus, Triticuside A may be a potentially useful wheat bran component that can be used for prevention or treatment of breast cancer.

[243]

TÍTULO / TITLE: - Effects of 5-Fluorouracil on Oxidative Stress and Calcium Levels in the Blood of Patients with Newly Diagnosed Colorectal Cancer.

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

REVISTA / JOURNAL: - Biol Trace Elem Res. 2013 Aug 29.

●● Enlace al texto completo (gratis o de pago) [1007/s12011-013-9795-4](#)

AUTORES / AUTHORS: - Kocer M; Naziroglu M

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Medical Faculty, Suleyman Demirel University, Isparta, Turkey.

RESUMEN / SUMMARY: - The administration of chemotherapeutic agents for colorectal carcinoma is associated with an increase in oxidative stress and a concomitant decrease in antioxidant and element levels in the blood. This study investigated the effects of 5-fluorouracil (5-FU) chemotherapy on the levels of lipid peroxidation, reduced glutathione (GSH), glutathione peroxidase (GSH-Px), antioxidant vitamins, and elements in colorectal cancer patients. Twelve patients with newly diagnosed colorectal carcinoma and 12 healthy subjects were included in this study. Blood samples were collected from both the healthy controls and patients. 5-FU was intravenously administered to the patients for 6 weeks, and blood samples were collected again from the treatment group. In the patient group, lipid peroxidation levels were increased in both the plasma and erythrocyte samples, whereas GSH-Px activity and concentrations of GSH, vitamin E, and beta-carotene in erythrocytes were decreased. The oxidant, antioxidant, and plasma calcium values were lower in 5-FU-treated patients than in the controls. Plasma vitamin A, chloride, sodium, and

potassium concentrations did not change with 5-FU treatment. In conclusion, oxidative stress in patients with newly diagnosed colorectal cancer is attributable to the disease and not to 5-FU treatment. Blood vitamin E, beta-carotene, GSH, and GSH-Px levels could be useful as early biomarkers of the prognosis of colorectal cancer patients.

[244]

TÍTULO / TITLE: - A single nucleotide polymorphism on the GALNT14 gene as an effective predictor of response to chemotherapy in advanced hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 19. doi: 10.1002/ijc.28439.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28439](#)

AUTORES / AUTHORS: - Yeh CT; Liang KH; Lin CC; Chang ML; Hsu CL; Hung CF

INSTITUCIÓN / INSTITUTION: - Liver Research Unit, Department of Hepato-Gastroenterology, Chang Gung Memorial Hospital, Taipei, Taiwan; Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan.

RESUMEN / SUMMARY: - Previously, a pilot genome-wide association study has identified candidate single nucleotide polymorphism predictors for the therapeutic response of 5-fluorouracil, mitoxantrone and cisplatin (FMP) combination chemotherapy in advanced hepatocellular carcinoma (HCC). Here, we conducted a prospective confirmatory study to examine the predictive value of rs9679162 (located on GALNT14 gene) for the therapeutic responses using a split-dose FMP protocol. One hundred and seven advanced HCC patients receiving split-dose FMP therapy were enrolled. All patients were in Barcelona Clinical Liver Cancer Stage C with either main portal vein thrombosis and/or distant metastasis. Of them, 105 (98.1%) were Child-Pugh classification B. GALNT14 genotype was determined before therapy. Of the patients included, 28 were rs9679162 "TT" and 79 were "non-TT" ("GG" + "GT") genotype. The median overall survival, time-to-progression, response rate and disease control rate were ("TT" versus "non-TT") 6.8 versus 3.9 months ($p < 0.001$), 3.9 versus 2.1 months ($p < 0.001$), 28.6% versus 10.1% ($p = 0.029$) and 35.7% versus 15.2% ($p = 0.030$), respectively. Multivariate analysis indicated that rs9679162 genotype was an independent predictor for overall survival ($p = 0.002$). Categorical analysis showed that 17 patients with "TT" genotype, tumor size < 10 cm and neutrophils $< 74\%$ had a median overall survival of 25.5 months and a therapeutic response rate of 47.1%. In conclusion, this prospective study confirmed that GALNT14 genotype (rs9679162) was an effective predictor for therapeutic outcome in advanced HCC patients treated by FMP chemotherapy. Combining GALNT14 genotype and clinical parameters, a subgroup of patients with excellent outcome was identified.

[245]

TÍTULO / TITLE: - Farnesyltransferase inhibitor tipifarnib inhibits Rheb prenylation and stabilizes Bax in acute myelogenous leukemia cells.

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

REVISTA / JOURNAL: - Haematologica. 2013 Aug 30.

●● Enlace al texto completo (gratis o de pago) 3324/haematol.2013.087734

AUTORES / AUTHORS: - Ding H; McDonald JS; Yun S; Schneider PA; Peterson KL; Flatten KS; Loegering DA; Oberg AL; Riska SM; Huang S; Sinicrope FA; Adjei AA; Karp JE; Meng XW; Kaufmann SH

INSTITUCIÓN / INSTITUTION: - USA;

RESUMEN / SUMMARY: - Although farnesyltransferase inhibitors have shown promising activity in relapsed lymphoma and sporadic activity in acute myelogenous leukemia, their mechanism of cytotoxicity is incompletely understood, making development of predictive biomarkers difficult. In the present study, we examined the action of tipifarnib in human acute myelogenous leukemia cell lines and clinical samples. In contrast to the Ras/MEK/ERK pathway-mediated Bim upregulation that is responsible for tipifarnib-induced killing of malignant lymphoid cells (H. Ding et al., Cytotoxicity of farnesyltransferase inhibitors in lymphoid cells mediated by MAPK pathway inhibition and Bim upregulation. Blood. 2011;118:4872-4881), inhibition of Rheb-induced mTOR signaling followed by dose-dependent upregulation of Bax and Puma occurred in acute myelogenous leukemia cell lines undergoing tipifarnib-induced apoptosis. Similar Bax and Puma upregulation occurred in serial bone marrow samples harvested from a subset of acute myelogenous leukemia patients during tipifarnib treatment. Expression of FTI-resistant Rheb M184L, like knockdown of Bax or Puma, diminished tipifarnib-induced killing. Further analysis demonstrated that increased Bax and Puma levels reflect protein stabilization rather than increased gene expression. In U937 cells selected for tipifarnib resistance, neither inhibition of signaling downstream of Rheb nor Bax and Puma stabilization occurred. Collectively, these results not only identify a pathway downstream from Rheb that contributes to tipifarnib cytotoxicity in human acute myelogenous leukemia cells, but also demonstrate that FTI-induced killing of lymphoid versus myeloid cells reflects distinct biochemical mechanisms downstream of different farnesylated substrates.

[246]

TÍTULO / TITLE: - 6-Thioguanine Induces Mitochondrial Dysfunction and Oxidative DNA Damage in Acute Lymphoblastic Leukemia Cells.

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

REVISTA / JOURNAL: - Mol Cell Proteomics. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) 1074/mcp.M113.029595

AUTORES / AUTHORS: - Zhang F; Fu L; Wang Y

INSTITUCIÓN / INSTITUTION: - University of California Riverside, United States;

RESUMEN / SUMMARY: - Thiopurines are among the most successful chemotherapeutic agents that are used for treating various human diseases, including acute lymphoblastic leukemia (ALL) and chronic inflammation. Although metabolic conversion and subsequent incorporation of 6-thioguanine (SG) nucleotides into nucleic acids are considered important for the thiopurine drugs to elicit their cytotoxic effects, alternative mechanisms may also exist. We hypothesized that an unbiased analysis of SG-induced perturbation of the entire proteome might uncover novel mechanism(s) of action of the drug. Herein we performed a quantitative assessment of global protein expression in control and SG-treated Jurkat-T cells by employing stable isotope labeling by amino acids in cell culture (SILAC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. LC-MS/MS quantification results uncovered substantially decreased expression of a large number of proteins in mitochondrial respiratory chain complex, and the Ingenuity Pathway Analysis of the significantly altered proteins showed that SG treatment induced mitochondrial dysfunction. This was accompanied with diminished uptake of MitoTracker Deep Red and elevated formation of oxidatively induced DNA lesions, including 8,5'-cyclo-2'-deoxyadenosine and 8,5'-cyclo-2'-deoxyguanosine. Together, our results suggested that SG may exert its cytotoxic effect by inducing mitochondrial dysfunction and reactive oxygen species formation in ALL cells.

[247]

TÍTULO / TITLE: - Bryostatin 5 induces apoptosis in acute monocytic leukemia cells by activating PUMA and caspases.

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

REVISTA / JOURNAL: - Eur J Pharmacol. 2013 Sep 11. pii: S0014-2999(13)00602-X. doi: 10.1016/j.ejphar.2013.08.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejphar.2013.08.012](https://doi.org/10.1016/j.ejphar.2013.08.012)

AUTORES / AUTHORS: - Wang Y; Zhang J; Wang Q; Zhang T; Yang Y; Yang F; Gao G; Dong H; Zhu H; Li Y; Lin H; Tang H; Chen X

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Xijing Hospital, Fourth Military Medical University, 127 Changle West Road, Xi'an 710032, China.

RESUMEN / SUMMARY: - Acute leukemia is a malignant clonal hematopoietic stem cell disease. In the current study, we examined the effects of bryostatin 5 on acute monocytic leukemia cells in vitro and in vivo. We also explored the mechanisms and pathways underlying the increase in apoptosis induced by bryostatin 5. Bryostatin 5 inhibited the growth of primary acute monocytic leukemia cells and U937 cells in a dose- and time-dependent manners. Bryostatin 5 also induced an increase in apoptosis and a decrease in the mitochondrial membrane potential (MMP) in U937 cells. Transmission electron microscopy (TEM) revealed that bryostatin 5-treated cells displayed typical apoptotic characteristics (chromatin condensation, karyopyknosis and

formation of crescents and apoptotic bodies). In addition, bryostatin 5 increased the expression of P53 upregulated modulator of apoptosis (PUMA) and slightly increased P53 expression. Bryostatin 5 also significantly decreased Bcl-XL expression and significantly increased the expression levels of Bak, Bax, cleaved caspase 9 and cleaved caspase 3. The pro-apoptotic activity of bryostatin 5 in U937 cells was inhibited by PUMA siRNA and z-LEHD-fmk (a specific caspase 9 inhibitor). In addition, the PUMA siRNA significantly affected the expression of cleaved caspase 9, whereas z-LEHD-fmk had little effect on the expression of PUMA. The results suggest that PUMA is located upstream of caspase 9 in this apoptotic signaling pathway. These novel findings provide mechanistic insight into the induction of apoptosis by bryostatin 5 and might facilitate the development of clinical strategies to enhance the therapeutic efficacy of treatments for acute monocytic leukemia.

[248]

TÍTULO / TITLE: - Accessory Cells of the Microenvironment Protect Multiple Myeloma from T Cell Cytotoxicity through Cell Adhesion-Mediated Immune Resistance.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 4.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-12-3676](#)

AUTORES / AUTHORS: - de Haart SJ; van de Donk NW; Minnema MC; Huang JH; Aarts-Riemens T; Bovenschen N; Yuan H; Groen RW; McMillin DW; Jakubikova J; Lokhorst HM; Martens A; Mitsiades CS; Mutis T

INSTITUCIÓN / INSTITUTION: - Laboratory of clinical chemistry and hematology, hemato-oncology, University Medical Center Utrecht.

RESUMEN / SUMMARY: - **PURPOSE** Cellular immunotherapy frequently fails to induce sustained remissions in multiple myeloma (MM) patients, indicating the ability of MM cells to evade cellular immunity. Toward a better understanding and effective therapeutic modulation of MM immune evasion mechanisms, we here investigated the role of the tumor microenvironment in rendering MM cells resistant to the cytotoxic machinery of T cells. **EXPERIMENTAL DESIGN** Using a compartment-specific, bioluminescence imaging-based assay system, we measured the lysis of luciferase-transduced MM cells by CD4+ or CD8+ cytotoxic T cells (CTLs) in the presence versus absence of adherent accessory cells of the bone marrow microenvironment. We simultaneously determined the level of CTL activation by measuring the granzyme B release in culture supernatants. **RESULTS** Bone marrow stromal cells from MM patients and healthy individuals as well as vascular endothelial cells significantly inhibited the lysis of MM cells in a cell-cell contact dependent manner and without substantial T cell suppression, thus demonstrating the induction of a cell adhesion-mediated immune resistance (CAM-IR) against CTL lysis. Further analyses revealed that adhesion to accessory cells down-regulated Fas and up-regulated the caspase 3-inhibitor survivin in

MM cells. Reconstitution of Fas expression with bortezomib enhanced the CTL-mediated lysis of MM cells. Repressing survivin with the small molecule YM155 synergized with CTLs and abrogated CAM-IR in vitro and in vivo. CONCLUSION These results reveal the cell adhesion-mediated induction of apoptosis resistance as a novel immune escape mechanism and provide a rationale to improve the efficacy of cellular therapies by pharmacological modulation of CAM-IR.

[249]

TÍTULO / TITLE: - Predictive value of sphingosine kinase 1 expression in neoadjuvant treatment of breast cancer.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Oct;139(10):1681-9. doi: 10.1007/s00432-013-1490-5. Epub 2013 Aug 18.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1490-5](#)

AUTORES / AUTHORS: - Ruckhaberle E; Karn T; Denkert C; Loibl S; Ataseven B; Reimer T; Becker S; Holtrich U; Rody A; Darb-Esfahani S; Nekljudova V; von Minckwitz G

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Goethe University Frankfurt, Theodor-Stern Kai 7, 60590, Frankfurter, Germany.

RESUMEN / SUMMARY: - PURPOSE: Sphingolipids play important roles in apoptosis and cell proliferation. Sphingosine kinase 1 (SphK1) expression has a prognostic impact in primary breast cancer, but its predictive value is currently unknown. METHODS: A total of 112 breast cancer specimens from a prospective neoadjuvant chemotherapy trial (GeparDuo) were studied. Using tissue microarrays of pre-treatment core cut biopsies, we determined the expression of SphK1 by immunohistochemistry. The upper quartile of the cohort according to an immune reactive score of SphK1 was used as cutoff for high expression. RESULTS: We observed a larger number of samples with high SphK1 expression among ER-negative cancers (36.8 vs. 20.5 % among ER-positive cancers; Fisher test $p = 0.073$). Eighteen of the 112 patients demonstrated a pathological complete response. A significant predictive value for pathological complete response was observed for ER negativity ($p = 0.003$), young age ($p = 0.037$), and high tumor grade ($p = 0.049$). An increased pCR rate was observed in tumors with high SphK1 expression within the luminal subtype (26.7 vs. 5.8 %; Fisher test $p = 0.040$). No significant difference in survival was detected according to SphK1 expression. CONCLUSIONS: Our results suggest that SphK1 may be a predictive factor for pCR after neoadjuvant treatment in luminal type breast cancers and warrants further investigation.

[250]

TÍTULO / TITLE: - Pertuzumab for the treatment of human epidermal growth factor receptor type 2-positive metastatic breast cancer.

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

REVISTA / JOURNAL: - Am J Health Syst Pharm. 2013 Sep 15;70(18):1579-87. doi: 10.2146/ajhp120735.

●● Enlace al texto completo (gratis o de pago) [2146/ajhp120735](#)

AUTORES / AUTHORS: - Chung C; Lam MS

INSTITUCIÓN / INSTITUTION: - Clement Chung, Pharm. D., BCOP, BCPS, is Oncology Clinical Pharmacist, Lyndon B. Johnson General Hospital, Harris Health System, Houston, TX; at the time of writing, he was Oncology Clinical Pharmacist, Kennewick General Hospital, Kennewick, WA. Masha S. H. Lam, Pharm. D., is Oncology Clinical Pharmacist, Hematology/Oncology Infusion Clinic, Kaiser Permanente, Antioch, CA.

RESUMEN / SUMMARY: - **PURPOSE:** The pharmacology, pharmacokinetics, clinical efficacy, safety, and administration of pertuzumab in patients with metastatic human epidermal growth factor receptor type 2 (HER2)-positive breast cancer are reviewed. **SUMMARY:** Disease progression in HER2-positive breast cancer is often due to resistance to or a lack of efficacy of trastuzumab-based anti-HER2 therapy. Pertuzumab is the first humanized monoclonal antibody in a new class of drugs, the HER dimerization inhibitors, approved by the Food and Drug Administration for the first-line treatment of patients with metastatic HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Since pertuzumab binds to a different epitope than trastuzumab, combination therapy with pertuzumab and trastuzumab results in a more complete blockade of HER2 signaling than trastuzumab monotherapy. The efficacy of adding pertuzumab to trastuzumab-docetaxel dual therapy was demonstrated in a pivotal randomized multicenter Phase III trial, which showed a significant benefit in terms of progression-free survival, with improved overall survival, in favor of the triple therapy as an initial regimen in treatment-naïve patients with metastatic HER2-positive breast cancer. The combination of pertuzumab and trastuzumab has been found to have a tolerable toxicity profile. As clinical trials of pertuzumab for adjuvant, neoadjuvant, and metastatic-disease treatment continue, its role in the treatment of HER2-positive breast cancer will continue to evolve. **CONCLUSION:** Pertuzumab, a novel HER2 dimerization inhibitor, has been shown to be effective in the treatment of metastatic HER2-positive breast cancer when used in combination with trastuzumab and docetaxel and is recommended for first-line therapy.

[251]

TÍTULO / TITLE: - Mast cells expressing interleukin 17 in the muscularis propria predict a favorable prognosis in esophageal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Cancer Immunol Immunother. 2013 Oct;62(10):1575-85. doi: 10.1007/s00262-013-1460-4. Epub 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1007/s00262-013-1460-4](https://doi.org/10.1007/s00262-013-1460-4)

AUTORES / AUTHORS: - Wang B; Li L; Liao Y; Li J; Yu X; Zhang Y; Xu J; Rao H; Chen S; Zhang L; Zheng L

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China, Cancer Center, Sun Yat-sen (Zhongshan) University, Guangzhou, 510 060, People's Republic of China.

RESUMEN / SUMMARY: - The proinflammatory cytokine interleukin 17 (IL-17) is considered to play a crucial role in diverse human tumors; however, its role in disease progression remains controversial. This study investigated the cellular source and distribution of IL-17 in esophageal squamous cell carcinoma (ESCC) in situ and determined its prognostic value. Immunohistochemistry, immunofluorescence and immunoelectron microscopy were used to identify IL-17-expressing cells in ESCC tissues, paying particular attention to their anatomic localization. Kaplan-Meier analysis and Cox proportional hazards regression models were applied to estimate overall survival in 215 ESCC patients with long-term follow-up (>10 years). The results showed that mast cells, but not T cells or macrophages, were the predominant cell type expressing IL-17 in ESCC tissues. Unexpectedly, these IL-17(+) cells were highly enriched in the muscularis propria rather than the corresponding tumor nest ($p < 0.0001$). The density of IL-17(+) cells in muscularis propria was inversely associated with tumor invasion ($p = 0.016$) and served as an independent predictor of favorable survival ($p = 0.007$). Moreover, the levels of IL-17(+) cells in muscularis propria were positively associated with the density of effector CD8(+) T cells and activated macrophages in the same area (both $p < 0.0001$). This finding suggested that mast cells may play a significant role in tumor immunity by releasing IL-17 at a previously unappreciated location, the muscularis propria, in ESCC tissues, which could serve as a potential prognostic marker and a novel therapeutic target for ESCC.

[252]

TÍTULO / TITLE: - A study of embryonic stem cell-related proteins in human astrocytomas: Identification of Nanog as a predictor of survival.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 19. doi: 10.1002/ijc.28441.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28441](https://doi.org/10.1002/ijc.28441)

AUTORES / AUTHORS: - Elsir T; Edqvist PH; Carlson J; Ribom D; Bergqvist M; Ekman S; Popova SN; Alafuzoff I; Ponten F; Nister M; Smits A

INSTITUCIÓN / INSTITUTION: - Department of Neuroscience, Neurology, Uppsala University, University Hospital, S-751 85 Uppsala; Karolinska Institutet, Department of

Oncology-Pathology, CCK R8:05, Karolinska University Hospital, S-17176 Stockholm, Sweden.

RESUMEN / SUMMARY: - Recent studies suggest that the regulatory networks controlling the functions of stem cells during development may be abnormally active in human cancers. An embryonic stem cell (ESC) gene signature was found to correlate with a more undifferentiated phenotype of several human cancer types including gliomas, and associated with poor prognosis in breast cancer. In the present study, we used tissue microarrays of 80 low-grade (WHO grade II) and 98 high-grade human gliomas (WHO grade III and IV) to investigate the presence of the ESC-related proteins Nanog, Klf4, Oct4, Sox2 and c-Myc by immunohistochemistry. While similar patterns of co-expressed proteins between low- and high-grade gliomas were present, we found up-regulated protein levels of Nanog, Klf4, Oct4 and Sox2 in high-grade gliomas. Survival analysis by Kaplan-Meier analysis revealed a significant shorter survival in the subgroups of low-grade astrocytomas (n=42) with high levels of Nanog protein (p=0.0067) and of Klf4 protein (p=0.0368), in high-grade astrocytomas (n=85) with high levels of Nanog (p=0.0042), Klf4 (p=0.0447), and c-Myc (p=0.0078) and in glioblastomas only (n=71) with high levels of Nanog (p=0.0422) and of c-Myc (p=0.0256). In the multivariate model, Nanog was identified as an independent prognostic factor in the subgroups of low-grade astrocytomas (p=0.0039), high-grade astrocytomas (p=0.0124) and glioblastomas only (p=0.0544), together with established clinical variables in these tumors. These findings provide further evidence for the joint regulatory pathways of ESC-related proteins in gliomas and identify Nanog as one of the key players in determining clinical outcome of human astrocytomas. © 2013 Wiley Periodicals, Inc.

[253]

TÍTULO / TITLE: - CK2 inhibitor CX4945 induces sequential inactivation of proteins in the signaling pathways related with cell migration and suppresses metastasis of A549 human lung cancer cells.

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

REVISTA / JOURNAL: - Bioorg Med Chem Lett. 2013 Oct 15;23(20):5609-13. doi: 10.1016/j.bmcl.2013.08.043. Epub 2013 Aug 17.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.08.043](https://doi.org/10.1016/j.bmcl.2013.08.043)

AUTORES / AUTHORS: - Ku MJ; Park JW; Ryu BJ; Son YJ; Kim SH; Lee SY

INSTITUCIÓN / INSTITUTION: - Department of Life Science, Gachon University, San 65, Bokjeong-Dong, Sujeong-Gu, Seongnam-Si, Gyeonggi-Do 461-701, Republic of Korea.

RESUMEN / SUMMARY: - Casein kinase 2 (CK2) is known to be involved in various cellular processes such as cell cycle, apoptosis and proliferation. It has been reported that the inhibition of CK2 induced by recently developed small molecule CX4945 shows anti-cancer effects including anti-proliferation and anti-angiogenesis in several different

cancers including prostate cancer. Here we report that migration and invasion of A549 human lung cancer cells are suppressed by the inhibition of CK2 induced by CX4945. We found that CX4945 sequentially attenuates the proteins in PI3K/Akt and MAPK pathways, two signaling pathways related with cell migration. This sequential control of signal pathways inhibits the expression of membrane type 1-matrix metalloproteinase and this leads to the selective attenuation of one of the gelatinases, MMP-2, which can degrade components of extracellular matrix, and metastasis of A549 human lung cancer cell.

[254]

TÍTULO / TITLE: - Reduced-intensity conditioning therapy with fludarabine, idarubicin, busulfan and cytarabine for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia and myelodysplastic syndrome.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Sep 5. pii: S0145-2126(13)00298-1. doi: 10.1016/j.leukres.2013.08.016.

●● Enlace al texto completo (gratis o de pago) 1016/j.leukres.2013.08.016

AUTORES / AUTHORS: - Gao L; Gao L; Gong Y; Zhang C; Chen XH; Zhang X

INSTITUCIÓN / INSTITUTION: - Department of Hematology for Xinqiao Hospital Affiliated to the Third Military Medical University, Shaping District of Chongqing 400037, People's Republic of China.

RESUMEN / SUMMARY: - We retrospectively analyzed allogeneic stem cell transplantation (allo-SCT) outcomes in 82 patients with AML or MDS were conditioned with fludarabine, idarubicin, intravenous-busulfan and cytarabine (FIBA) or busulfan and cyclophosphamide (BuCy). Compared to BuCy regimen, reduced intensity conditioning (RIC) with FIBA was associated with a lower incidence of severe acute GVHD, lower NRM and a similar relapse rate. There was no significant difference in the 3 year overall survival (OS), but this is possibly due to the limited number of patients. The FIBA regimen is promising to replace BuCy regimen because of better security and similar relapse rate.

[255]

TÍTULO / TITLE: - Clinical and laboratory studies of the novel cyclin-dependent kinase inhibitor dinaciclib (SCH 727965) in acute leukemias.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Oct;72(4):897-908. doi: 10.1007/s00280-013-2249-z. Epub 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) 1007/s00280-013-2249-z

AUTORES / AUTHORS: - Gojo I; Sadowska M; Walker A; Feldman EJ; Iyer SP; Baer MR; Sausville EA; Lapidus RG; Zhang D; Zhu Y; Jou YM; Poon J; Small K; Bannerji R

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Marlene and Stewart Greenebaum Cancer Center, University of Maryland, Baltimore, MD, USA, igojo1@jhmi.edu.

RESUMEN / SUMMARY: - PURPOSE: Dinaciclib inhibits cyclin-dependent kinases 1, 2, 5, and 9 with a better therapeutic index than flavopiridol in preclinical studies. This study assessed the activity of dinaciclib in acute leukemia both in the clinic and in vitro. METHODS: Adults with relapsed/refractory acute myeloid leukemia (n = 14) and acute lymphoid leukemia (n = 6) were treated with dinaciclib 50 mg/m² given as a 2-h infusion every 21 days. RESULTS: Most patients had dramatic but transient reduction in circulating blasts; however, no remissions were achieved on this schedule. The most common toxicities were gastrointestinal, fatigue, transaminitis, and clinical and laboratory manifestations of tumor lysis syndrome, including one patient who died of acute renal failure. Dinaciclib pharmacokinetics showed rapid (2 h) achievement of maximum concentration and a short elimination/distribution phase. Pharmacodynamic studies demonstrated in vivo inhibition of Mcl-1 expression and induction of PARP cleavage in patients' peripheral blood mononuclear cells 4 h after dinaciclib infusion, but the effects were lost by 24 h and did not correlate with clinical outcome. Correlative in vitro studies showed that prolonged exposures to dinaciclib, at clinically attainable concentrations, result in improved leukemia cell kill. CONCLUSIONS: While dinaciclib given as a 2-h bolus did not exhibit durable clinical activity, pharmacokinetic and pharmacodynamic data support the exploration of prolonged infusion schedules in future trials in patients with acute leukemias.

[256]

TÍTULO / TITLE: - Prognostic implications of histologic grade and intensity of Bcl-2 expression in follicular lymphomas undergoing rituximab-containing therapy.

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

REVISTA / JOURNAL: - Hum Pathol. 2013 Jul 31. pii: S0046-8177(13)00267-0. doi: 10.1016/j.humpath.2013.06.013.

●● Enlace al texto completo (gratis o de pago) 1016/j.humpath.2013.06.013

AUTORES / AUTHORS: - Maeshima AM; Taniguchi H; Nomoto J; Miyamoto KI; Fukuhara S; Munakata W; Maruyama D; Kim SW; Watanabe T; Kobayashi Y; Tobinai K; Tsuda H

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, 104-0045 Tokyo, Japan. Electronic address: akmaeshi@ncc.go.jp.

RESUMEN / SUMMARY: - This study aimed to determine the correlations of 7 histopathologic prognostic indicators of follicular lymphoma (follicular lymphoma grade, CD10 expression, Bcl-2 expression, IGH/BCL2 fusion, diffuse area, fibrosis, and

marginal zone differentiation) with progression-free survival, overall survival, and follicular lymphoma histologic grade in 255 follicular lymphoma patients who were treated with rituximab-containing therapy. The complete response, overall response, 6-year progression-free survival, and 6-year overall survival rates were 83%, 96%, 56%, and 97%, respectively. Patients with follicular lymphoma grades 3^a and 3^b showed 100% 6-year and 10-year overall survival, and progression-free survival did not significantly differ between patients with follicular lymphoma grade 3 and those with follicular lymphoma grades 1 and 2. The absence or presence of Bcl-2 expression and intensity of Bcl-2 expression were not significant prognostic indicators of progression-free survival and overall survival. Likewise, the presence of IGH/BCL2 fusion, diffuse area, fibrosis, and marginal zone differentiation were not significantly correlated with progression-free survival and overall survival. Follicular lymphoma grade 3 was correlated with nodal disease and negative or lower intensity of Bcl-2 expression, but not with age, stage, or IGH/BCL2 status. In the prerituximab era, grade 3 disease was reported to be associated with a poor prognosis; however, the opposite was true for patients treated with rituximab-containing therapy, regardless of their age or disease stage. Bcl-2 expression and marginal zone differentiation were not prognostic indicators in follicular lymphoma patients treated with rituximab-containing therapy.

[257]

TÍTULO / TITLE: - Src kinases in chondrosarcoma chemoresistance and migration: dasatinib sensitises to doxorubicin in TP53 mutant cells.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1214-22. doi: 10.1038/bjc.2013.451. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.451](https://doi.org/10.1038/bjc.2013.451)

AUTORES / AUTHORS: - van Oosterwijk JG; van Ruler MA; Briaire-de Bruijn IH; Herpers B; Gelderblom H; van de Water B; Bovee JV

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands.

RESUMEN / SUMMARY: - Background:Chondrosarcomas are malignant cartilage-forming tumours of bone. Because of their resistance to conventional chemotherapy and radiotherapy, currently no treatment strategies exist for unresectable and metastatic chondrosarcoma. Previously, PI3K/AKT/GSK3beta and Src kinase pathways were shown to be activated in chondrosarcoma cell lines. Our aim was to investigate the role of these kinases in chemoresistance and migration in chondrosarcoma in relation to TP53 mutation status.Methods:We used five conventional and three dedifferentiated chondrosarcoma cell lines and investigated the effect of PI3K/AKT/GSK3beta pathway inhibition (enzastaurin) and Src pathway inhibition (dasatinib) in chemoresistance using WST assay and live cell imaging with AnnexinV staining. Immunohistochemistry

on tissue microarrays (TMAs) containing 157 cartilaginous tumours was performed for Src family members. Migration assays were performed with the RTCA xCelligence System. Results: Src inhibition was found to overcome chemoresistance, to induce apoptosis and to inhibit migration. Cell lines with TP53 mutations responded better to combination therapy than wild-type cell lines (P=0.002). Tissue microarray immunohistochemistry confirmed active Src (pSrc) signalling, with Fyn being most abundantly expressed (76.1%). Conclusion: These results strongly indicate Src family kinases, in particular Fyn, as a potential target for the treatment of inoperable and metastatic chondrosarcomas, and to sensitise for doxorubicin especially in the presence of TP53 mutations.

[258]

TÍTULO / TITLE: - Enhancement of baicalin by hexamethylene bisacetamide on the induction of apoptosis contributes to simultaneous activation of the intrinsic and extrinsic apoptotic pathways in human leukemia cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2071-80. doi: 10.3892/or.2013.2684. Epub 2013 Aug 21.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2684](#)

AUTORES / AUTHORS: - Ren X; Zhang Y; Li C; Wang H; Jiang Z; Zhang Z; Guo Q; Song G; Bi K; Jiang G

INSTITUCIÓN / INSTITUTION: - Key Laboratory for Rare and Uncommon Diseases, Key Laboratory for Tumor Immunology and Chinese Medicine Immunology of Shandong Province, Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan, Shandong, P.R. China.

RESUMEN / SUMMARY: - Hexamethylene bisacetamide (HMBA) and natural flavanoid baicalin both exert potent antileukemic activity. However, there is currently no data on the anti-leukemic effects of baicalin in combination with HMBA. In the present study, we demonstrated that the combination of baicalin and HMBA synergistically inhibited the proliferation of acute myeloid leukemia (AML) cell lines. In addition, a slight G0/G1 phase arrest and significant apoptosis were observed. The combination treatment triggered apoptosis through the intrinsic pathway, which involved loss of MMP, decreased Bcl2/Bax ratio and BclXL/Bax ratio, caspase9 activation, as well as through the extrinsic pathway mediated by Fas and caspase8 activation. On the other hand, combination of baicalin and HMBA showed little toxic effect on peripheral blood mononuclear cells from healthy volunteers. Our results raise the possibility that the novel combination of baicalin and HMBA may be a promising regimen for the treatment of AML.

[259]

TÍTULO / TITLE: - Predicting Response to Bevacizumab in Ovarian Cancer: A Panel of Potential Biomarkers Informing Treatment Selection.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 15;19(18):5227-5239. Epub 2013 Aug 9.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-0489](#)

AUTORES / AUTHORS: - Collinson F; Hutchinson M; Craven RA; Cairns DA; Zougman A; Wind TC; Gahir N; Messenger MP; Jackson S; Thompson D; Adusei C; Ledermann JA; Hall G; Jayson GC; Selby PJ; Banks RE

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds; St James's Institute of Oncology, Bexley Wing; Cancer Research UK Centre, Leeds Institute of Molecular Medicine, St James's University Hospital; Department of Clinical Biochemistry and Immunology, Leeds General Infirmary, Leeds; MRC Clinical Trials Unit; UCL Cancer Institute, University College, London; and Christie Hospital, University of Manchester, Withington, Manchester, United Kingdom.

RESUMEN / SUMMARY: - **PURPOSE:** The aim of this study was to identify and validate novel predictive and/or prognostic serum proteomic biomarkers in patients with epithelial ovarian cancer (EOC) treated as part of the phase III international ICON7 clinical trial. **EXPERIMENTAL DESIGN:** ICON7 was a phase III international trial in EOC which showed a modest but statistically significant benefit in progression-free survival (PFS) with the addition of bevacizumab to standard chemotherapy. Serum samples from 10 patients who received bevacizumab (five responders and five nonresponders) were analyzed by mass spectrometry to identify candidate biomarkers. Initial validation and exploration by immunoassay was undertaken in an independent cohort of 92 patients, followed by a second independent cohort of 115 patients (taken from across both arms of the trial). **RESULTS:** Three candidate biomarkers were identified: mesothelin, fms-like tyrosine kinase-4 (FLT4), and alpha1-acid glycoprotein (AGP). Each showed evidence of independent prognostic potential when adjusting for high-risk status in initial ($P < 0.02$) and combined ($P < 0.01$) validation cohorts. In cohort I, individual biomarkers were not predictive of bevacizumab benefit; however, when combined with CA-125, a signature was developed that was predictive of bevacizumab response and discriminated benefit attributable to bevacizumab better than clinical characteristics. The signature showed weaker evidence of predictive ability in validation cohort II, but was still strongly predictive considering all samples ($P = 0.001$), with an improvement in median PFS of 5.5 months in signature-positive patients in the experimental arm compared with standard arm. **CONCLUSIONS:** This study shows a discriminatory signature comprising mesothelin, FLT4, AGP, and CA-125 as potentially identifying those patients with EOC more likely to benefit from bevacizumab. These results require validation in further patient cohorts. Clin Cancer Res; 19(18); 5227-39. ©2013 AACR.

[260]

TÍTULO / TITLE: - PIAS3 activates the intrinsic apoptotic pathway in non-small cell lung cancer cells independent of p53 status.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 19. doi: 10.1002/ijc.28448.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28448](#)

AUTORES / AUTHORS: - Dabir S; Kluge A; McColl K; Liu Y; Lam M; Halmos B; Wildey G; Dowlati A

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Case Western Reserve University, Cleveland, Ohio 44106.

RESUMEN / SUMMARY: - Protein inhibitor of activated STAT3 (PIAS3) is an endogenous inhibitor of STAT3 that negatively regulates STAT3 transcriptional activity and cell growth and demonstrates limited expression in the majority of human squamous cell carcinomas of the lung. In the present study we sought to determine if PIAS3 inhibits cell growth in non-small cell lung cancer (NSCLC) cell lines by inducing apoptosis. Our results demonstrate that over-expression of PIAS3 promotes mitochondrial depolarization, leading to cytochrome c release, caspase 9 and 3 activation and PARP cleavage. This intrinsic pathway activation was associated with decreased Bcl-xL expression and increased Noxa expression and was independent of p53 status. Furthermore, PIAS3 inhibition of STAT3 activity was also p53 independent. Microarray experiments were performed to discover STAT3-independent mediators of PIAS3-induced apoptosis by comparing the apoptotic gene expression signature induced by PIAS3 over-expression with that induced by STAT3 siRNA. The results showed that a subset of apoptotic genes was uniquely expressed only after PIAS3 expression. Thus, PIAS3 may represent a promising lung cancer therapeutic target because of its p53-independent efficacy as well as its potential to synergize with Bcl-2 targeted inhibitors. © 2013 Wiley Periodicals, Inc.

[261]

TÍTULO / TITLE: - Bortezomib induces apoptosis and autophagy in osteosarcoma cells through mitogen-activated protein kinase pathway in vitro.

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

REVISTA / JOURNAL: - J Int Med Res. 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1177/0300060513490618](#)

AUTORES / AUTHORS: - Lou Z; Ren T; Peng X; Sun Y; Jiao G; Lu Q; Zhang S; Lu X; Guo W

INSTITUCIÓN / INSTITUTION: - Musculoskeletal Tumour Centre, People's Hospital, Peking University, Beijing, China.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate the effects of bortezomib on human osteosarcoma cells from the HOS cell line, and the underlying associated mechanisms. METHODS: Viability of HOS cells treated with bortezomib (5-20 nM) for different time periods was measured and changes in the cell cycle were assessed. Apoptosis and autophagy in HOS cells treated with bortezomib were analysed using annexin V-fluorescein isothiocyanate assay, transmission electron microscopy and Western blotting. Surges in mitogen-activated protein kinase (MAPK) pathways including MAPK/extracellular signal-regulated kinase (ERK) kinase (MEK1/2), ERK1/2, c-Jun N-terminal kinase (JNK) and p38 MAPK were analysed using Western blotting. RESULTS: Bortezomib induced growth inhibition in a time- and dose-dependent manner, and autophagy and apoptosis in a dose-dependent manner, in HOS cells. HOS cell autophagy and apoptosis in response to bortezomib, corresponded with changing levels of intracellular MAPK signalling molecules. CONCLUSIONS: This study provided new insights into the mechanisms underlying bortezomib-induced apoptosis in human osteosarcoma HOS cells, and suggests that bortezomib could be a potent chemotherapeutic agent in the treatment of osteosarcoma.

[262]

TÍTULO / TITLE: - Anthracene-bisphosphonate based novel fluorescent organic nanoparticles explored as apoptosis inducers of cancer cells.

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

REVISTA / JOURNAL: - Chem Commun (Camb). 2013 Oct 21;49(82):9461-3. doi: 10.1039/c3cc44989k.

●● Enlace al texto completo (gratis o de pago) [1039/c3cc44989k](#)

AUTORES / AUTHORS: - Pramanik M; Chatterjee N; Das S; Saha KD; Bhaumik A

INSTITUCIÓN / INSTITUTION: - Department of Materials Science, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India. msab@iacs.res.in.

RESUMEN / SUMMARY: - We report the first synthesis and use of a well defined fluorescent organic nanoparticle (FON), tetraethyl anthracene-9,10-diyl-9,10-bis(phosphonate) [TEABP], as a selective anticancer candidate by apoptosis mediated cancer therapy towards U937 cells together with its unique solvatochromic properties.

[263]

TÍTULO / TITLE: - Analytic and Clinical Validation of a Prostate Cancer-Enhanced Messenger RNA Detection Assay in Whole Blood as a Prognostic Biomarker for Survival.

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

REVISTA / JOURNAL: - Eur Urol. 2013 Jul 26. pii: S0302-2838(13)00721-5. doi: 10.1016/j.eururo.2013.07.006.

●● Enlace al texto completo (gratuito o de pago) 1016/j.eururo.2013.07.006

AUTORES / AUTHORS: - Danila DC; Anand A; Schultz N; Heller G; Wan M; Sung CC; Dai C; Khanin R; Fleisher M; Lilja H; Scher HI

INSTITUCIÓN / INSTITUTION: - Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Department of Medicine, Weill Cornell Medical College, New York, NY, USA.

RESUMEN / SUMMARY: - BACKGROUND: Biomarkers based on detecting prostate cancer (PCa)-specific transcripts in blood are associated with inferior outcomes, but their validation in a clinical context is lacking. OBJECTIVE: To determine whether detecting enhanced transcripts for PCa in whole blood using an analytically valid assay has prognostic significance relative to circulating tumor cell (CTC) enumeration. DESIGN, SETTING, AND PARTICIPANTS: The detection of KLK3, KLK2, HOXB13, GRHL2, and FOXA1 in whole blood by reverse transcription polymerase chain reaction (RT-PCR) was studied in 97 men with metastatic castration-resistant PCa (mCRPC) as a prognostic factor for overall survival. INTERVENTION: The 2.5ml of blood was collected in PAXgene tubes for total RNA extraction and 7.5ml for CTC enumeration from patients with progressive mCRPC. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: PCa-enriched genes were detected using a sensitive RT-PCR assay in whole blood from patients with mCRPC. Analytical validity of the assay was established in a clinical laboratory environment. The frequency of detecting transcripts was compared to CTC enumeration using CellSearch in an independent data set and survival associations were explored by concordance probability estimate (CPE). RESULTS AND LIMITATIONS: Two or more genes were detected by PCR in 53% of patients (51 of 97; 95% confidence interval [CI], 43-63%), and unfavorable CTC counts (five or more cells) were seen in 46% (45 of 97; 95% CI, 36-56%). Importantly, transcripts were detectable in 11 of 52 patients with favorable CTC counts (21%; 95% CI, 8-35%). Transcript detection predicted overall survival in a proportional hazards model. Significantly, the predictive accuracy of RT-PCR detection in combination with CTC enumeration had a CPE of 0.752 (standard error: 0.038), although this was limited by the number of patients evaluated. CONCLUSIONS: This validated RT-PCR assay detecting prostate-specific RNA in whole blood is prognostic for survival and may assess patient risk in tandem with CellSearch CTC enumeration. Its clinical utility is being prospectively explored.

[264]

TÍTULO / TITLE: - Molecular targeting of Akt by thymoquinone promotes G arrest through translation inhibition of cyclin D1 and induces apoptosis in breast cancer cells.

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

REVISTA / JOURNAL: - Life Sci. 2013 Sep 15. pii: S0024-3205(13)00521-3. doi: 10.1016/j.lfs.2013.09.009.

●● Enlace al texto completo (gratuito o de pago) [1016/j.lfs.2013.09.009](https://doi.org/10.1016/j.lfs.2013.09.009)

AUTORES / AUTHORS: - Rajput S; Kumar BN; Dey KK; Pal I; Parekh A; Mandal M

INSTITUCIÓN / INSTITUTION: - School of Medical Science and Technology, Indian Institute of Technology Kharagpur, Kharagpur 721302, West Bengal, India.

RESUMEN / SUMMARY: - AIM: Thymoquinone (TQ), the predominant bioactive constituent of black seed oil (*Nigella Sativa*), has been shown to possess antineoplastic activity against multifarious tumors. However, the meticulous mechanism of TQ on Akt mediated survival pathway is still unrevealed in breast cancer. Here, we investigated TQ's mechanism of action against PI3K/Akt signaling and its downstream targets by modulating proteins translational machinery, leading to apoptosis in cancer cells. MAIN METHODS: MDA-MB-468 and T-47D cells were treated with TQ and evaluated for its anticancer activity through phase distribution and western blot. Modulatory effects of TQ on Akt were affirmed through kinase and drug potential studies. KEY FINDINGS: Studies revealed G1 phase arrest till 24h incubation with TQ while extended exposure showed phase shift to subG1 indicating apoptosis, supported by suppression of cyclin D1, cyclin E and cyclin dependent kinase inhibitor p27 expression. Immunoblot and membrane potential studies revealed mitochondrial impairment behind apoptotic process with upregulation of Bax, cytoplasmic cytochrome c and procaspase-3, PARP cleavage along with Bcl-2, Bcl-xL and survivin downregulation. Moreover, we construed the rationale behind mitochondrial dysfunction by examining the phosphorylation status of PDK1, PTEN, Akt, c-raf, GSK-3beta and Bad in TQ treated cells, thus ratifying the involvement of Akt in apoptosis. Further, the consequential effect of Akt inhibition by TQ is proven by translational repression through deregulated phosphorylation of 4E-BP1, eIF4E, S6R and p70S6K. SIGNIFICANCE: Our observations for the first time may provide a new insight for the development of novel therapies for Akt overexpressed breast cancer by TQ.

[265]

TÍTULO / TITLE: - Role of tumor necrosis factor alpha-induced protein 1 in paclitaxel resistance.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1016/j.onc.2013.299)

REVISTA / JOURNAL: - Oncogene. 2013 Aug 5. doi: 10.1038/onc.2013.299.

●● Enlace al texto completo (gratuito o de pago) [1038/onc.2013.299](https://doi.org/10.1038/onc.2013.299)

AUTORES / AUTHORS: - Zhu Y; Yao Z; Wu Z; Mei Y; Wu M

INSTITUCIÓN / INSTITUTION: - Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science and Technology of China, Anhui, China.

RESUMEN / SUMMARY: - Paclitaxel has been extensively used as an antitumor drug to treat a broad range of epithelial cancers, including breast and cervical cancers. However, the efficacy of this drug is greatly limited by the development of acquired

resistance. Identification of the underlying resistance mechanisms may inform the development of new therapies that elicit long-term response of tumors to paclitaxel treatment. Here we report that increased expression of TNFAIP1 (tumor necrosis factor alpha-induced protein 1) confers acquired resistance to paclitaxel. TNFAIP1 is shown to compete with paclitaxel for binding to beta-tubulin, thereby preventing paclitaxel-induced tubulin polymerization, cell cycle arrest and ultimate cell death. We also show that expression of TNFAIP1 is regulated by the transcriptional factor Sp1. In a xenograft mouse model, increased expression of TNFAIP1 decreases, whereas knockdown of TNFAIP1 increases tumor response to paclitaxel. Therefore, these results reveal tnfaip1 as a novel paclitaxel-resistance associated gene and suggest that TNFAIP1 may represent a valuable therapeutic target for the treatment of cancer. Oncogene advance online publication, 5 August 2013; doi:10.1038/onc.2013.299.

[266]

TÍTULO / TITLE: - STMN-1 Gene: A Predictor of Survival in Stage IIA Esophageal Squamous Cell Carcinoma After Ivor-Lewis Esophagectomy?

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3215-z](#)

AUTORES / AUTHORS: - Akhtar J; Wang Z; Yu C; Zhang ZP; Bi MM

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Provincial Hospital Affiliated to Shandong University, Shandong, China.

RESUMEN / SUMMARY: - BACKGROUND: Prognosis of esophageal squamous cell carcinoma (ESCC) is stage-specific; however, some patients with the same stage have different survival outcomes. Clinically, it is significant to explore the biological marker to predict patient's outcome. We investigated the association between the stathmin1 gene (STMN-1) expression and the prognosis of patients who underwent Ivor-Lewis esophagectomy. METHODS: A total of 162 patients who suffered from midthoracic stage IIA ESCC and completely resected with Ivor-Lewis esophagectomy were studied for STMN-1 expression by qRT-PCR in fresh-frozen tissue and validated by immunohistochemistry in matched formalin fixed-paraffin embedded tissue samples. STMN-1 level was evaluated as a prognostic factor in ESCC. SPSS 21.0 software was used to analyze the relationship between STMN-1 expression and clinicopathological characteristics and survival probability. RESULTS: The overall 3- and 5-year survival was 72.20 and 42.00 % respectively. Ninety-four patients (58.02 %) experienced disease recurrence with a disease-free interval of 21.50 +/- 1.20 months. qRT-PCR result showed that STMN-1 mRNA level in patients who were alive at the end of follow-up was lower compared with patients who died during the follow-up period ($p < 0.05$). Immunohistochemical results showed that 94 patients had STMN-1 protein

overexpression (58.02 %), patient with STMN-1 overexpression had worse survival compared with patients who had low STMN-1 expression ($p = 0.00$). Cox regression analysis revealed that STMN-1 protein expression and T classification are independent prognostic factors. CONCLUSIONS: Even localized ESCC are potential to relapse with poor prognosis. This study demonstrates that STMN-1 level is an independent prognostic factor after Ivor-Lewis esophagectomy. In addition, assessment of STMN-1 level could improve stratification of stage IIA ESCC patients.

[267]

TÍTULO / TITLE: - Loss of androgen receptor expression predicts early recurrence in triple-negative and basal-like breast cancer.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Aug 9. doi: 10.1038/modpathol.2013.145.

●● Enlace al texto completo (gratis o de pago) [1038/modpathol.2013.145](https://doi.org/10.1038/modpathol.2013.145)

AUTORES / AUTHORS: - Thike AA; Yong-Zheng Chong L; Cheok PY; Li HH; Wai-Cheong Yip G; Huat Bay B; Tse GM; Iqbal J; Tan PH

INSTITUCIÓN / INSTITUTION: - [1] Department of Pathology, Singapore General Hospital, Singapore, Singapore [2] Department of Clinical Research, Singapore General Hospital, Singapore, Singapore [3] Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore [4] Department of Anatomical and Cellular Pathology, Chinese University of Hong Kong, Hong Kong, China.

RESUMEN / SUMMARY: - Treatment of triple-negative invasive breast cancers, defined by the absence of estrogen and progesterone receptors and c-erbB2 expression, remains challenging. Androgen receptor, a member of the nuclear receptor superfamily that is involved in signaling pathways regulating cell proliferation, has been implicated in breast tumorigenesis. We immunohistochemically examined the expression of androgen receptor, basal markers (CK14, 34betaE12) and EGFR in 699 triple-negative invasive breast cancers in tissue microarrays using the streptavidin-biotin method, and correlated the findings with clinical outcome. Positive androgen receptor expression was defined as staining of 1% or more of tumor cell nuclei. Survival outcomes were estimated with the Kaplan-Meier method and compared between groups with log-rank statistics. Cox proportional hazards models were used to determine the effect of androgen receptor on survival outcomes. Immunohistochemical positivity was observed in 38% of tumors, with the proportion of stained tumor cells ranging from 1 to 95% (mean 29%, median 10%). Androgen receptor expression was inversely associated with histologic grade and mitotic score. CK14, 34betaE12 and EGFR confirmed 85% of cases to be basal-like, without significant association of basal-like phenotype with androgen receptor expression. Disease-free survival was significantly better in androgen receptor-positive triple-negative breast cancer, with a trend for improved overall survival. Decreased recurrence likelihood in both triple-negative and

basal-like tumors (hazard ratio, 0.704; 95% confidence intervals, 0.498-0.994; P=0.0464; and hazard ratio, 0.675; 95% confidence intervals, 0.468-0.974; P=0.0355, respectively) was noted within 5 years of diagnosis but not thereafter. Our study suggests that loss of androgen receptor in triple-negative breast cancers augurs a worse prognosis, including those with basal-like features. More work in elucidating its relationship with mechanisms of progression, as well as trials of targeted treatment for androgen receptor-expressing triple-negative tumors, needs to be performed. Modern Pathology advance online publication, 9 August 2013; doi:10.1038/modpathol.2013.145.

[268]

TÍTULO / TITLE: - Alpha-tomatine synergises with paclitaxel to enhance apoptosis of androgen-independent human prostate cancer PC-3 cells in vitro and in vivo.

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

REVISTA / JOURNAL: - Phytomedicine. 2013 Aug 3. pii: S0944-7113(13)00246-8. doi: 10.1016/j.phymed.2013.07.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.phymed.2013.07.002](#)

AUTORES / AUTHORS: - Lee ST; Wong PF; Hooper JD; Mustafa MR

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, 50603 Kuala Lumpur, Malaysia.

RESUMEN / SUMMARY: - Alpha (alpha)-tomatine, a major saponin found in tomato has been shown to inhibit the growth of androgen-independent prostate cancer PC-3 cells. The effects of alpha-tomatine in combination with the chemotherapeutic agent paclitaxel against PC-3 cells were investigated in the present study. Combined treatment with a sub-toxic dose of alpha-tomatine and paclitaxel significantly decreased cell viability with concomitant increase in the percentage of apoptotic PC-3 cells. The combined treatment, however, had no cytotoxic effect on the non-neoplastic prostate RWPE-1 cells. Apoptosis of PC-3 cells was accompanied by the inhibition of PI3K/Akt pro-survival signaling, an increase in the expression of the pro-apoptotic protein BAD but a decrease in the expressions of anti-apoptotic proteins, Bcl-2 and Bcl-xL. Results from a mouse xenograft model showed the combined treatment completely suppressed subcutaneous tumor growth without significant side effects. Consistent with its in vitro anti-cancer effects, tumor materials from mice showed increased apoptosis of tumor cells with reduced protein expression of activated PI3K/Akt. These results suggest that the synergistic anti-cancer effects of paclitaxel and alpha-tomatine may be beneficial for refractory prostate cancer treatment.

[269]

TÍTULO / TITLE: - Reply to Letter: A Role for Adjuvant RFA in Managing Hepatic Metastases From Gastrointestinal Stromal Tumors (GIST) After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors.

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

REVISTA / JOURNAL: - Cardiovasc Intervent Radiol. 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1007/s00270-013-0671-6](#)

AUTORES / AUTHORS: - Hakime A; Le Cesne A; Deschamps F; Farouil G; Domont J; De Baere T

INSTITUCIÓN / INSTITUTION: - Gustave Roussy Institute, 39 r Camille Desmoulins, 94805, Villejuif, France, thakime@yahoo.com.

[270]

TÍTULO / TITLE: - Role of C-Arm CT for Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: Diagnostic Performance and Predictive Value for Therapeutic Response Compared With Gadoteric Acid-Enhanced MRI.

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

REVISTA / JOURNAL: - AJR Am J Roentgenol. 2013 Sep;201(3):675-83. doi: 10.2214/AJR.12.10445.

●● Enlace al texto completo (gratis o de pago) [2214/AJR.12.10445](#)

AUTORES / AUTHORS: - Yu MH; Kim JH; Yoon JH; Kim HC; Chung JW; Han JK; Choi BI

INSTITUCIÓN / INSTITUTION: - 1 Department of Radiology, Seoul National University Hospital, 101 Daehang-no, Jongno-gu, Seoul 110-744, Republic of Korea.

RESUMEN / SUMMARY: - OBJECTIVE. The objective of our study was to investigate the diagnostic performance of C-arm CT and its value to predict response of hepatocellular carcinoma (HCC) to trans-catheter arterial chemoembolization (TACE) compared with gadoteric acid-enhanced MRI. MATERIALS AND METHODS. Sixty-eight patients with HCCs (n = 167; 145 > 1 cm, 22 ≤ 1 cm) underwent both C-arm CT immediately before TACE and gadoteric acid-enhanced MRI within 2 weeks before TACE. Two radiologists rated the possibility of HCC using a 5-point confidence scale focused on the degree of arterial enhancement and the shape of the lesion seen on C-arm CT. They also graded the possibility of HCC on MRI based on the signal intensities on T1- and T2-weighted images, arterial enhancement, and hypointensity on both the late phase and the hepatobiliary phase. We also measured the apparent diffusion coefficient value. The diagnostic accuracy was evaluated using the alternative free-response receiver operating characteristic curve method. A multivariate logistic regression analysis was performed between the good-response and nonresponse HCCs for TACE. RESULTS. The diagnostic accuracy of MRI was greater than that of C-arm CT (0.890 vs 0.681, respectively; p < 0.001). However, in small HCCs (≤ 1 cm), C-arm CT showed a higher sensitivity than MRI (90.9% vs 70.5%, respectively; p = 0.023) and a lower positive predictive value than MRI (40.8% vs 57.4%, p = 0.073). Well-defined strong arterial

enhancement on C-arm CT (odds ratio = 8.08, $p = 0.05$) was statistically significant for predicting therapeutic response of HCC to TACE. CONCLUSION. C-arm CT showed greater sensitivity than gadoteric acid-enhanced MRI in depicting small HCCs (≤ 1 cm). Furthermore, well-defined strong arterial enhancement on C-arm CT can be used to predict therapeutic response of HCC to TACE.

[271]

TÍTULO / TITLE: - DZNep, inhibitor of S-adenosylhomocysteine hydrolase, down-regulates expression of SETDB1 H3K9me3 HMTase in human lung cancer cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 6;438(4):647-52. doi: 10.1016/j.bbrc.2013.07.128. Epub 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.07.128](#)

AUTORES / AUTHORS: - Lee JK; Kim KC

INSTITUCIÓN / INSTITUTION: - Medical and Bio-Material Research Center, Department of Biological Sciences, College of Natural Sciences, Kangwon National University, Chuncheon 200-701, Republic of Korea.

RESUMEN / SUMMARY: - 3-Deazaneplanocin A (DZNep), an epigenetic anticancer drug, leads to the indirect suppression of S-adenosyl methionine-dependent cellular methylations by inhibiting S-adenosyl homocystein (AdoHcy) hydrolase. Although it is well known that DZNep targets the degradation of EZH2 protein, H3K27me3 HMTase, there are still uncertainties about the regulation of other types of HMTases during cell death. In this study, we describe that SETDB1 gene expression was regulated by DZNep treatment in human lung cancer cells. We confirm that DZNep induced growth inhibition and increased the dead cell population of lung cancer cells. DZNep treatment affected histone methylations, including H3K27me3 and H3K9me3, but not H3K4me3. Reduced levels of H3K27me3 and H3K9me3 were related with the decreased EZH2 and SETDB1 proteins. Real time PCR analysis showed that SETDB1 gene expression was decreased by DZNep treatment, but no effect was observed for EZH2 gene expression. We cloned the promoter region of SETDB1 and SUV39H1 genes, and performed luciferase assays. The promoter activity of SETDB1 gene was down regulated by DZNep treatment, whereas no effect on SUV39H1 promoter activity was observed. In conclusion, we suggest that DZNep regulates not only on H3K27me3 HMTase EZH2, but also H3K9 HMTase SETDB1 gene expression at the transcription level, implicating that the mechanism of action of DZNep targets multiple HMTases during the death of lung cancer cells.

[272]

TÍTULO / TITLE: - A novel long non-coding RNA T-ALL-R-LncR1 knockdown and Par-4 cooperate to induce cellular apoptosis in T-cell acute lymphoblastic leukemia cells.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) 3109/10428194.2013.829574

AUTORES / AUTHORS: - Zhang L; Xu HG; Lu C

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

RESUMEN / SUMMARY: - T-cell acute lymphoblastic leukemia (T-ALL) is a hematologic malignancy with a poor prognosis. It has been shown that long non-coding RNA (lncRNA) plays an important role in tumorigenesis. Here, we characterized a novel lncRNA, T-ALL-R-LncR1, with whole-transcriptome deep sequencing from the Jurkat leukemic T-cell line. T-ALL-R-LncR1 was not observed in human normal tissues. However, an obvious expression was observed in some tumor tissues. T-ALL-R-LncR1 was markedly expressed in neoplastic T lymphocytes of 11 cases out of 21 children with T-ALL, indicating that T-ALL-R-LncR1 might be associated with T-ALL. T-ALL-R-LncR1 knockdown predisposed Jurkat cells to undergo pro-apoptotic factor Par-4-induced apoptosis. Further studies revealed that T-ALL-R-LncR1 knockdown facilitated the formation of a Par-4/THAP1 protein complex, resulting in the activation of caspase-3 and an increase of pro-apoptotic Smac protein in T-ALL cells. Our studies indicate a potential role of suppressing the novel long non-coding RNA T-ALL-R-LncR1 in the therapy of human T-ALL.

[273]

TÍTULO / TITLE: - Regulation of Id1 expression by epigallocatechin-3-gallate and its effect on the proliferation and apoptosis of poorly differentiated AGS gastric cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1052-8. doi: 10.3892/ijo.2013.2043. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) 3892/ijo.2013.2043

AUTORES / AUTHORS: - Ma J; Shi M; Li G; Wang N; Wei J; Wang T; Wang Y

INSTITUCIÓN / INSTITUTION: - Department of Geriatrics, Shanghai Changning Central Hospital, Shanghai 200336, P.R. China.

RESUMEN / SUMMARY: - We investigated the inhibition of apoptosis and proliferation of poorly differentiated AGS gastric cancer cells by epigallocatechin-3-gallate (EGCG), to establish target genes for regulation by EGCG. The proliferation and apoptosis of AGS gastric cancer cells treated with EGCG were observed by cell counting kit (CCK)-8 and flow cytometry. Differential gene expression in AGS cells treated with EGCG was screened by gene expression microarrays. Id1 gene and protein expression were determined by quantitative PCR and western blot analysis. The effect of Id1 on EGCG-

induced apoptosis and cell cycle arrest of AGS cells was verified with RNAi. The proliferation and apoptosis of AGS cells treated with siRNA_{Id1} was observed by CCK-8 and flow cytometry. EGCG significantly promoted apoptosis and inhibited the proliferation of AGS cells. The Id1 gene was differentially expressed in AGS cells treated with EGCG, and Id1 mRNA and protein were downregulated in AGS cells treated with EGCG, confirmed by quantitative PCR and western blot analysis. Id1 mRNA and protein were also downregulated in AGS cells treated with siRNA-Id1. The apoptosis and proliferation of AGS cells treated with siRNA-Id1 were similar to those in cells treated with EGCG. EGCG induces apoptosis and inhibits proliferation of poorly differentiated AGS gastric cancer cells, and Id1 may be one of the target genes regulated by EGCG in cancer inhibition.

[274]

TÍTULO / TITLE: - Plasma Monocyte Chemoattractant Protein-1 and Tumor Necrosis Factor-alpha Levels Predict the Presence of Coronary Artery Calcium in HIV-Infected Individuals Independent of Traditional Cardiovascular Risk Factors.

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

REVISTA / JOURNAL: - AIDS Res Hum Retroviruses. 2013 Sep 21.

●● [Enlace al texto completo \(gratis o de pago\) 1089/AID.2013.0183](#)

AUTORES / AUTHORS: - Shikuma CM; Barbour JD; Ndhlovu LC; Keating SM; Norris PJ; Budoff M; Parikh N; Seto T; Gangcuangco LM; Ogata-Arakaki D; Chow D

INSTITUCIÓN / INSTITUTION: - 1 University of Hawaii, Honolulu, Hawaii.

RESUMEN / SUMMARY: - Abstract Coronary artery calcium (CAC) is a validated subclinical measure of atherosclerosis. Studies in the general population have linked blood inflammatory biomarkers including monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor (TNF)-alpha with the burden of CAC, but this relationship is often lost following correction for traditional cardiovascular risk factors. We assessed the relationship of various biomarkers to CAC, specifically in HIV-infected individuals on potent antiretroviral therapy (ART). Analyses utilized entry data from participants in the Hawaii Aging with HIV-Cardiovascular (HAHC-CVD) study. Computerized tomography examinations for CAC were obtained locally and analyzed by a central reading center in blinded fashion. Plasma biomarkers were assessed by multiplexing using Milliplex Human Cardiovascular Disease panels. Among a cohort of 130 subjects [88% male, median (IQR) age of 51 (46-57) years, CD4 count of 492 (341-635) cells/mm³, 86.9% with HIV RNA \leq 50 copies/ml], CAC was present in 46.9% of subjects. In univariate analyses higher levels of log-transformed MCP-1 and TNF-alpha were associated with the presence of CAC ($p < 0.05$). In multivariate logistic regression models, MCP-1 and TNF-alpha remained significant after adjustment for traditional cardiovascular (CVD) risk factors. Similar results were found when analyses were assessed by Framingham risk score categories or when restricted to subjects with

plasma HIV RNA \leq 50 copies/ml. In contrast to findings in the general population, higher MCP-1 and TNF- α predict the presence of CAC independent of traditional CVD risk factors in HIV-infected subjects fully suppressed on ART, suggesting that HIV-mediated immune activation may play a role in CVD risk.

[275]

TÍTULO / TITLE: - Depletion of end-binding protein 1 (EB1) promotes apoptosis of human non-small-cell lung cancer cells via reactive oxygen species and Bax-mediated mitochondrial dysfunction.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Oct 1;339(1):15-24. doi: 10.1016/j.canlet.2013.07.027. Epub 2013 Jul 27.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.07.027](https://doi.org/10.1016/j.canlet.2013.07.027)

AUTORES / AUTHORS: - Kim MJ; Yun HS; Hong EH; Lee SJ; Baek JH; Lee CW; Yim JH; Kim JS; Park JK; Um HD; Hwang SG

INSTITUCIÓN / INSTITUTION: - Division of Radiation Cancer Biology, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea.

RESUMEN / SUMMARY: - Although end-binding protein 1 (EB1) is well known to regulate microtubule dynamics, the role of EB1 in apoptosis of non-small cell lung cancer (NSCLC) is poorly understood. Here, we investigated the molecular mechanism by which EB1 regulates apoptosis in H460, A549, and H1299 cells. Depletion of EB1 in A549 and H1299 cells, which express high levels of EB1, induced cell death in a p53-independent manner through over-production of reactive oxygen species (ROS) and Bax induction. This phenomenon was potentiated in radiation-treated EB1-knockdown cells and was largely blocked by N-acetyl-L-cysteine, a scavenger of ROS. ROS accelerated the activation of nuclear factor-kappa B (NF-kappaB) to promote transcriptional activity of Bax, an action that was accompanied by cytochrome c translocation and apoptosis-inducing factor (AIF) release. The NF-kappaB inhibitor, BAY 11-7082, potently inhibited the apoptosis induced by EB1 knockdown and radiation treatment, in association with diminished activity of the mitochondrial death pathway. Conversely, ectopic overexpression of EB1 in H460 cells, which express low levels of EB1, remarkably abrogated radiation-induced apoptosis and NF-kappaB-mediated mitochondrial dysfunction. Our data provide the first demonstration that down-regulation of EB1 promotes NSCLC cell death by inducing ROS-mediated, NF-kappaB-dependent Bax signaling cascades, a process in which cytochrome c and AIF play important roles, indicating a potential therapeutic benefit of EB1 in lung cancer.

[276]

TÍTULO / TITLE: - Soluble Interleukin-6 Receptor is a Prognostic Marker for Relapse-Free Survival in Estrogen Receptor-Positive Breast Cancer.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Oct;31(8):516-521. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.826239](https://doi.org/10.3109/07357907.2013.826239)

AUTORES / AUTHORS: - Won HS; Kim YA; Lee JS; Jeon EK; An HJ; Sun DS; Ko YH; Kim JS

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu-si, Gyeonggi-do, Korea, 1.

RESUMEN / SUMMARY: - Considering the protumorigenic roles of interleukin-6 (IL-6) transsignaling, we assessed the serum levels of IL-6, soluble interleukin-6 receptor (sIL-6R), and soluble glycoprotein 130 (sgp130) in 143 patients with breast cancer. Serum levels of IL-6 were elevated with advanced T and N stage. Serum levels of sIL-6R were lower in patients with estrogen receptor-positive cancer. The median values of IL-6 and sgp130 did not differ between patients with recurrence and those without recurrence. However, higher serum levels of sIL-6R at diagnosis were associated with significantly shorter relapse-free survival in patients with estrogen receptor-positive breast cancer.

[277]

TÍTULO / TITLE: - Design, synthesis, and mechanistic investigations of bile Acid-tamoxifen conjugates for breast cancer therapy.

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

REVISTA / JOURNAL: - Bioconjug Chem. 2013 Sep 18;24(9):1468-84. doi: 10.1021/bc300664k. Epub 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1021/bc300664k](https://doi.org/10.1021/bc300664k)

AUTORES / AUTHORS: - Sreekanth V; Bansal S; Motiani RK; Kundu S; Muppu SK; Majumdar TD; Panjamurthy K; Sengupta S; Bajaj A

INSTITUCIÓN / INSTITUTION: - The Laboratory of Nanotechnology and Chemical Biology, Regional Centre for Biotechnology, 180 Udyog Vihar, Phase 1, Gurgaon-122016, Haryana, India.

RESUMEN / SUMMARY: - We have synthesized two series of bile acid tamoxifen conjugates using three bile acids lithocholic acid (LCA), deoxycholic acid (DCA), and cholic acid (CA). These bile acid-tamoxifen conjugates possess 1, 2, and 3 tamoxifen molecules attached to hydroxyl groups of bile acids having free acid and amine functionalities at the tail region of bile acids. The in vitro anticancer activities of these bile acid-tamoxifen conjugates show that the free amine headgroup based cholic acid-tamoxifen conjugate (CA-Tam3-Am) is the most potent anticancer conjugate as compared to the parent drug tamoxifen and other acid and amine headgroup based bile acid-tamoxifen conjugates. The cholic acid-tamoxifen conjugate (CA-Tam3-Am)

bearing three tamoxifen molecules shows enhanced anticancer activities in both estrogen receptor +ve and estrogen receptor -ve breast cancer cell lines. The enhanced anticancer activity of CA-Tam3-Am is due to more favorable irreversible electrostatic interactions followed by intercalation of these conjugates in hydrophobic core of membrane lipids causing increase in membrane fluidity. Annexin-FITC based FACS analysis showed that cells undergo apoptosis, and cell cycle analysis showed the arrest of cells in sub G0 phase. ROS assays showed a high amount of generation of ROS independent of ER status of the cell line indicating changes in mitochondrial membrane fluidity upon the uptake of the conjugate that further leads to the release of cytochrome c, a direct and indirect regulator of ROS. The mechanistic studies for apoptosis using PCR and western analysis showed apoptosis by intrinsic and extrinsic pathways in ER +ve MCF-7 cells and by only an intrinsic pathway in ER -ve cells. In vivo studies in the 4T1 tumor model showed that CA-Tam3-Am is more potent than tamoxifen. These studies showed that bile acids provide a new scaffold for high drug loading and that their anticancer activities strongly depend on charge and hydrophobicity of lipid-drug conjugates.

[278]

TÍTULO / TITLE: - Novel anthranilamide-pyrazolo[1,5-a]pyrimidine conjugates modulate the expression of p53-MYCN associated micro RNAs in neuroblastoma cells and cause cell cycle arrest and apoptosis.

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

REVISTA / JOURNAL: - Bioorg Med Chem Lett. 2013 Oct 15;23(20):5699-706. doi: 10.1016/j.bmcl.2013.08.018. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.08.018](#)

AUTORES / AUTHORS: - Ramaiah MJ; Pushpavalli SN; Lavanya A; Bhadra K; Haritha V; Patel N; Tamboli JR; Kamal A; Bhadra U; Pal-Bhadra M

INSTITUCIÓN / INSTITUTION: - Department of Chemical Biology, CSIR-Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad 500 007, India.

RESUMEN / SUMMARY: - It has previously been shown that anthranilamide-pyrazolo[1,5-a]pyrimidine conjugates activate p53 and cause apoptosis in cervical cancer cells such as HeLa and SiHa. Here we establish the role of these conjugates in activating p53 pathway by phosphorylation at Ser15, 20 and 46 residues and downregulate key oncogenic proteins such as MYCN and Mdm2 in IMR-32 neuroblastoma cells. Compounds decreased the proliferation rate of neuroblastoma cells such as IMR-32, Neuro-2^a, SK-N-SH. Compound treatment resulted in G2/M cell cycle arrest. The expression of p53 dependent genes such as p21, Bax, caspases was increased with concomitant decrease of the survival proteins as well as anti-apoptotic proteins such as Akt1, E2F1 and Bcl2. In addition the expression of important microRNAs such as miR-34^a, c, miR-200b, miR-107, miR-542-5p and miR-605 were significantly increased

that eventually lead to the activation of apoptotic pathway. Our data revealed that conjugates of this nature cause cell cycle arrest and apoptosis in IMR-32 cells [MYCN (+) with intact wild-type p53] by activating p53 signalling and provides a lead for the development of anti-cancer therapeutics.

[279]

TÍTULO / TITLE: - Combination of Ad-sTRAIL with the chemotherapeutic drug cisplatin synergistically enhances their pro-apoptotic ability in human breast cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Oct;30(4):1913-9. doi: 10.3892/or.2013.2653. Epub 2013 Aug 2.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2653](#)

AUTORES / AUTHORS: - Liu X; Wang J; Wang H; Liu S; Liang Y; Lv Z; Zhou Q; Ding W

INSTITUCIÓN / INSTITUTION: - Central Laboratory of Molecular Biology, The Affiliated Hospital of the Medical College, Qingdao University, Qingdao 266003, P.R. China.

RESUMEN / SUMMARY: - Tumor necrosis factor-related apoptosis-inducing ligand/Apo2 ligand (TRAIL or Apo2L) is a member of the tumor necrosis factor superfamily that induces apoptosis in various cancer cell types but not in most normal cells. However, it is clear that not all cancer cells are sensitive to the killing effects of TRAIL, including breast cancer. Previous studies have demonstrated that chemotherapeutic drugs sensitize tumor cells to apoptosis induced by TRAIL in several types of malignancies. In the present study, we studied the effects of TRAIL combined with cisplatin on two breast cancer cell lines MDA-MB-468 and HCC-1937 in vitro. MTT assay, crystal violet staining assay, DAPI staining assay and flow cytometric analysis were undertaken to evaluate the enhancement of breast cancer cell death using Ad-sTRAIL and/or cisplatin. The levels of apoptotic molecules in signal transduction pathways were analyzed by real-time RT-PCR and western blotting. We found that co-treatment with Ad-sTRAIL and cisplatin exhibited stronger cytotoxicity and induced more significant apoptosis in breast cancer cells compared with Ad-sTRAIL or cisplatin alone. Pretreatment with cisplatin significantly enhanced the expression of DR5. Moreover, the induction of apoptosis by TRAIL plus cisplatin was accompanied by the downregulation of cFLIP and BCL2L1, and simultaneously robust enzymatic activation of caspase-8, culminating in decreased cancer cell survival. The present study revealed that TRAIL conjugated with cisplatin exhibited a markedly increased cytotoxic and apoptosis-inducing effect on breast cancer cells.

[280]

TÍTULO / TITLE: - Different cytotoxicities and cellular localizations of novel quindoline derivatives with or without boronic acid modifications in cancer cells.

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

REVISTA / JOURNAL: - Chem Commun (Camb). 2013 Aug 27;49(76):8516-8. doi: 10.1039/c3cc45203d.

●● Enlace al texto completo (gratis o de pago) [1039/c3cc45203d](#)

AUTORES / AUTHORS: - Yin R; Zhang M; Hao C; Wang W; Qiu P; Wan S; Zhang L; Jiang T

INSTITUCIÓN / INSTITUTION: - School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao, China. jiangtao@ouc.edu.cn lijuanzhang@ouc.edu.cn.

RESUMEN / SUMMARY: - The synthesis of a 4 x 4 series of novel quindoline derivatives with or without boronic acid modifications and their cytotoxicities, cellular localizations, and implications on cancer cells are presented and discussed.

[281]

TÍTULO / TITLE: - Granzyme M as a novel effector molecule for human cytolytic fusion proteins: CD64-specific cytotoxicity of Gm-H22(scFv) against leukemic cells.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Aug 22. pii: S0304-3835(13)00578-8. doi: 10.1016/j.canlet.2013.08.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.08.005](#)

AUTORES / AUTHORS: - Schiffer S; Letzian S; Jost E; Mladenov R; Hristodorov D; Huhn M; Fischer R; Barth S; Thepen T

INSTITUCIÓN / INSTITUTION: - Department of Experimental Medicine and Immunotherapy, RWTH Aachen, Institute for Applied Medical Engineering, Aachen, Germany; Department of Pharmaceutical Product Development, Fraunhofer Institute for Molecular Biology and Applied Ecology, Aachen, Germany.

RESUMEN / SUMMARY: - Immunotoxins are promising targeted therapeutic agents comprising an antibody-based ligand that specifically binds to diseased cells, and a pro-apoptotic protein. Toxic components from bacteria or plants can trigger a neutralizing immune response, so that human effector molecules are more suitable. In this context, the protease granzyme B has been successfully tested in cytotoxicity assays against different cancer cells in vitro and in vivo. Our aim here was to introduce granzyme M as an alternative and novel component of human cytolytic fusion proteins. We fused it to the humanized single-chain antibody fragment (scFv) H22 which specifically binds to CD64, an FcγRI receptor overexpressed on activated myeloid cells and leukemic cells. We show that the humanized cytolytic fusion protein Gm-H22(scFv) specifically targets the acute myeloid leukemia cell line HL60 in vitro and is cytotoxic with an IC50 between 1.2 and 6.4 nM. These findings were confirmed ex vivo using leukemic primary cells from patients, which were killed by granzyme M despite the presence of the granzyme B inhibitor serpin B9. In conclusion, granzyme M is a promising new cell-death inducing component for hCFPs because it specifically and efficiently kills target cells when fused to a targeting component.

[282]

TÍTULO / TITLE: - Optimizing Screening for Tuberculosis and Hepatitis B Prior to Starting Tumor Necrosis Factor-alpha Inhibitors in Crohn's Disease.

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

REVISTA / JOURNAL: - Dig Dis Sci. 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1007/s10620-013-2820-9](#)

AUTORES / AUTHORS: - van der Have M; Oldenburg B; Fidder HH; Belderbos TD; Siersema PD; van Oijen MG

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology and Hepatology, University Medical Center Utrecht, PO Box 85500, 3500 GA, Utrecht, The Netherlands, M.vanderhave@umcutrecht.nl.

RESUMEN / SUMMARY: - BACKGROUND AND AIMS: Treatment with tumor necrosis factor-alpha (TNF-alpha) inhibitors in patients with Crohn's disease (CD) is associated with potentially serious infections, including tuberculosis (TB) and hepatitis B virus (HBV). We assessed the cost-effectiveness of extensive TB screening and HBV screening prior to initiating TNF-alpha inhibitors in CD. METHODS: We constructed two Markov models: (1) comparing tuberculin skin test (TST) combined with chest X-ray (conventional TB screening) versus TST and chest X-ray followed by the interferon-gamma release assay (extensive TB screening) in diagnosing TB; and (2) HBV screening versus no HBV screening. Our base-case included an adult CD patient starting with infliximab treatment. Input parameters were extracted from the literature. Direct medical costs were assessed and discounted following a third-party payer perspective. The main outcome was the incremental cost-effectiveness ratio (ICER). Sensitivity and Monte Carlo analyses were performed over wide ranges of probability and cost estimates. RESULTS: At base-case, the ICERs of extensive screening and HBV screening were <euro>64,340 and <euro>75,760 respectively to gain one quality-adjusted life year. Sensitivity analyses concluded that extensive TB screening was a cost-effective strategy if the latent TB prevalence is more than 12 % or if the false positivity rate of TST is more than 20 %. HBV screening became cost-effective if HBV reactivation or HBV-related mortality is higher than 37 and 62 %, respectively. CONCLUSIONS: Extensive TB screening and HBV screening are not cost-effective compared with conventional TB screening and no HBV screening, respectively. However, when targeted at high-risk patient groups, these screening strategies are likely to become cost-effective.

[283]

TÍTULO / TITLE: - The NR4A orphan nuclear receptors do not confer prednisolone resistance in pediatric acute lymphoblastic leukemia.

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

REVISTA / JOURNAL: - Leukemia. 2013 Sep 23. doi: 10.1038/leu.2013.275.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.275](#)

AUTORES / AUTHORS: - Aries IM; van den Dungen ER; Pieters R; den Boer ML

INSTITUCIÓN / INSTITUTION: - Department of Pediatric Oncology/Hematology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands.

[284]

TÍTULO / TITLE: - Distinguishing luminal breast cancer subtypes by Ki67, progesterone receptor or TP53 status provides prognostic information.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Sep 20. doi: 10.1038/modpathol.2013.153.

●● Enlace al texto completo (gratis o de pago) [1038/modpathol.2013.153](#)

AUTORES / AUTHORS: - Feeley LP; Mulligan AM; Pinnaduwage D; Bull SB; Andrulis IL

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Cork University Hospital, Cork, Ireland.

RESUMEN / SUMMARY: - The objectives of this study were to determine the prognostic significance of subgrouping estrogen receptor (ER)-positive breast tumors into low- and high-risk luminal categories using Ki67 index, TP53, or progesterone receptor (PR) status. The study group comprised 540 patients with lymph node negative, invasive breast carcinoma. Luminal A subtype was defined as being ER positive, HER2 negative, and Ki67 low (<14% cells positive) and luminal B subtype as being ER positive, HER2 negative, and Ki67 high (>=14% cells positive). Luminal tumors were also subgrouped into risk categories based on the PR and TP53 status. Survival analysis was performed. Patients with luminal B tumors (n=173) had significantly worse disease-free survival compared to those with luminal A tumors (n=186) (log rank P-value=0.0164; univariate Cox regression relative risk 2.00; 95% CI, 1.12-3.58; P=0.0187). Luminal subtype remained an independent prognostic indicator on multivariate analysis including traditional prognostic factors (relative risk 2.12; 95% CI, 1.16-3.88; P=0.0151). Using TP53 status or PR negativity rather than Ki67 to classify ER-positive luminal tumors gave similar outcome results to those obtained using the proliferation index. However, it was a combination of the three markers, which proved the most powerful prognostically. Ki67 index, TP53 status, or PR negativity can be used to segregate ER-positive, HER2-negative tumors into prognostically meaningful subgroups with significantly different clinical outcomes. These biomarkers particularly in combination may potentially be used clinically to guide patient management. Modern Pathology advance online publication, 20 September 2013; doi:10.1038/modpathol.2013.153.

[285]

TÍTULO / TITLE: - Post-surgical highly sensitive C-reactive protein and prognosis in early-stage breast cancer.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2694-8](#)

AUTORES / AUTHORS: - Tibau A; Ennis M; Goodwin PJ

INSTITUCIÓN / INSTITUTION: - Division of Medical Oncology and Hematology, Department of Medicine, Mount Sinai Hospital, 1284-600 University Avenue, Toronto, ON, M5G 1X5, Canada.

RESUMEN / SUMMARY: - Obesity, associated with inflammation, has been linked to poor prognosis in breast cancer. Research investigating the potential role of C-reactive protein (CRP), an obesity-associated systemic marker of inflammation, as a mediator of adverse prognostic effects of obesity has yielded inconsistent results. We examined the association of highly sensitive CRP (hsCRP) with obesity-related factors and breast cancer outcome. A cohort of 535 non-diabetic women diagnosed with T1-3, N0-1, M0 breast cancer, was assembled between 1989 and 1996 and followed prospectively. Circulating levels of hsCRP were analyzed on blood obtained postoperatively, prior to systemic therapy, in 501 women. Correlations and prognostic associations were analyzed using one-way analysis of variance, Spearman's rank correlation coefficients[®] and Cox models. hsCRP was significantly correlated with body mass index ($r = 0.60$), insulin ($r = 0.44$), leptin ($r = 0.54$), and lipids, but not T or N stage, grade or estrogen receptor/progesterone receptor. At a median follow-up of 12 years, hsCRP was not associated with distant disease-free survival or overall survival in univariable [Q4 vs. Q1 hazard ratio (HR) 1.03, 95 % confidence interval (CI) 0.69-1.52, $P = 0.9$ and HR 1.27, 95 % CI 0.86-1.86, $P = 0.24$, respectively] or multivariable [Q4 vs Q1 HR 1.02, 95 % CI 0.66-1.59, $P = 0.93$ and HR 1.17, 95 % CI 0.76-1.81, $P = 0.48$ respectively] analyses. hsCRP was associated with age, comorbidities, and the insulin resistance syndrome but not with breast cancer outcome.

[286]

TÍTULO / TITLE: - Highly efficient synthetic iron-dependent nucleases activate both intrinsic and extrinsic apoptotic death pathways in leukemia cancer cells.

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

REVISTA / JOURNAL: - J Inorg Biochem. 2013 Jul 19;128C:38-47. doi:

10.1016/j.jinorgbio.2013.07.019.

●● Enlace al texto completo (gratis o de pago) [1016/j.jinorgbio.2013.07.019](#)

AUTORES / AUTHORS: - Horn A Jr; Fernandes C; Parrilha GL; Kanashiro MM; Borges FV; de Melo EJ; Schenk G; Terenzi H; Pich CT

INSTITUCIÓN / INSTITUTION: - Laboratorio de Ciencias Químicas, Universidade Estadual do Norte Fluminense Darcy Ribeiro, Campos dos Goytacazes, 28013-602 RJ, Brazil.
Electronic address: adolfo@uenf.br.

RESUMEN / SUMMARY: - The nuclease activity and the cytotoxicity toward human leukemia cancer cells of iron complexes, $[\text{Fe}(\text{HPCINOL})\text{Cl}_2]\text{NO}_3$ (1), $[\text{Cl}(\text{HPCINOL})\text{Fe}(\mu\text{-O})\text{Fe}(\text{HPCINOL})\text{Cl}]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ (2), and $[(\text{SO}_4)(\text{HPCINOL})\text{Fe}(\mu\text{-O})\text{Fe}(\text{HPCINOL})(\text{SO}_4)] \cdot 6\text{H}_2\text{O}$ (3) (HPCINOL=1-(bis-pyridin-2-ylmethyl-amino)-3-chloropropan-2-ol), were investigated. Each complex was able to promote plasmid DNA cleavage and change the supercoiled form of the plasmid to circular and linear ones. Kinetic data revealed that (1), (2) and (3) increase the rate of DNA hydrolysis about 278, 192 and 339million-fold, respectively. The activity of the complexes was inhibited by distamycin, indicating that they interact with the minor groove of the DNA. The cytotoxic activity of the complexes toward U937, HL-60, Jukart and THP-1 leukemia cancer cells was studied employing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), fluorescence and electronic transmission microscopies, flow cytometry and a cytochrome C release assay. Compound (2) has the highest activity toward cancer cells and is the least toxic for normal ones (i.e. peripheral blood mononuclear cells (PBMCs)). In contrast, compound (1) is the least active toward cancer cells but displays the highest toxicity toward normal cells. Transmission electronic microscopy indicates that cell death shows features typical of apoptotic cells, which was confirmed using the annexin V-FITC/PI (fluorescein isothiocyanate/propidium iodide) assay. Furthermore, our data demonstrate that at an early stage during the treatment with complex (2) mitochondria lose their transmembrane potential, resulting in cytochrome C release. A quantification of caspases 3, 9 (intrinsic apoptosis pathway) and caspase 8 (extrinsic apoptosis pathway) indicated that both the intrinsic (via mitochondria) and extrinsic (via death receptors) pathways are involved in the apoptotic stimuli.

[287]

TÍTULO / TITLE: - Ribosomal s6 protein kinase 4: a prognostic factor for renal cell carcinoma.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 3;109(5):1137-46. doi: 10.1038/bjc.2013.463. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.463](https://doi.org/10.1038/bjc.2013.463)

AUTORES / AUTHORS: - Fan L; Li P; Yin Z; Fu G; Liao DJ; Liu Y; Zhu J; Zhang Y; Wang L; Yan Q; Guo Y; Shao C; Huang G; Wang Z

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Cancer Biology, Department of Pathology, Xijing Hospital, Fourth Military Medical University, Changle West Road #169, Xi'an 710032, China.

RESUMEN / SUMMARY: - Background: The expression and function of ribosomal s6 protein kinase 4 (RSK4) in renal cell carcinoma (RCC) are unknown. Methods: Immunohistochemistry was used to detect the expression of RSK4 in RCC, and the relationship between RSK4 expression and clinicopathological features as well as prognosis of RCC patients was statistically analysed. Ectopic RSK4 expression in RCC cell lines was performed to determine its effect on cell cycle regulation, tumour invasiveness, and metastatic capability. Results: RSK4 was overexpressed in RCCs ($P=0.003$), compared with normal tissues, and the expression varied in different RCC subtypes ($P=0.021$), especially in two subtypes of papillary RCCs ($P=0.001$). RSK4 expression was positively correlated with high pT stage ($P<0.001$), high Fuhrman grade ($P<0.001$), lymph node involvement ($P<0.001$), and presence of distant metastasis ($P=0.039$), and could predict poor outcome in RCC patients. Molecular studies showed that overexpression of RSK4 could promote cell cycle progression and enhance the invasive and metastatic capability of RCC cell lines and vice versa. Conclusion: The expression pattern and molecular mechanisms of RSK4 in RCCs indicate that it could be a potential independent prognostic factor and serve as a new potential therapeutic target for RCC patients.

[288]

TÍTULO / TITLE: - Effects of a combined treatment with tamoxifen and estrogen receptor beta agonists on human breast cancer cell lines.

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

REVISTA / JOURNAL: - Arch Gynecol Obstet. 2013 Aug 2.

●● Enlace al texto completo (gratis o de pago) [1007/s00404-013-2977-7](#)

AUTORES / AUTHORS: - Lattrich C; Schuler S; Haring J; Skrzypczak M; Ortmann O; Treack O

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RESUMEN / SUMMARY: - INTRODUCTION: Coexpression of estrogen receptors (ER) alpha and beta is present in about half of all breast cancer cases. Whereas ERalpha is a well-established target for endocrine therapy with the selective estrogen receptor modulator tamoxifen, the applicability of ERbeta as target in breast cancer therapy is unclear. In this study, we examined the effects of two synthetic ERbeta agonists alone and in combination with tamoxifen on ERalpha/beta-positive breast cancer cells. METHODS: We treated MCF-7 and T-47D breast cancer cells with the ERbeta agonists ERB-041 and WAY-200070 and measured the effects on cell growth. In addition, transcriptome analyses were performed by means of Affymetrix GeneChip arrays. RESULTS: When given alone, ERbeta agonists ERB-041 and WAY-200070 did not affect the growth of MCF-7 or T-47D cells. In contrast, addition of these drugs to tamoxifen

increased its growth-inhibitory effect on both cell lines. This effect was more pronounced under serum-free conditions, but was also observed in the presence of serum in T-47D cells. Transcriptome analyses revealed a set of genes regulated after addition of ERbeta agonists including S100A8 and CD177. CONCLUSION: The observed enhanced growth-inhibitory effects of a combination of tamoxifen and ERbeta agonists in vitro encourage further studies to test its possible use in the clinical setting.

[289]

TÍTULO / TITLE: - Erlotinib Response in an NSCLC Patient with a Novel Compound G719D+L861R Mutation in EGFR.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Sep;8(9):e83-4. doi: 10.1097/JTO.0b013e31829ceb8d.

●● Enlace al texto completo (gratis o de pago) [1097/JTO.0b013e31829ceb8d](#)

AUTORES / AUTHORS: - Berge EM; Aisner DL; Doebele RC

INSTITUCIÓN / INSTITUTION: - *Departments of Medicine, Division of Medical Oncology, daggerPathology, University of Colorado School of Medicine, Aurora, Colorado.

[290]

TÍTULO / TITLE: - Systems biology of Ewing sarcoma: a network model of EWS-FLI1 effect on proliferation and apoptosis.

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

REVISTA / JOURNAL: - Nucleic Acids Res. 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [1093/nar/gkt678](#)

AUTORES / AUTHORS: - Stoll G; Surdez D; Tirode F; Laud K; Barillot E; Zinovyev A; Delattre O

INSTITUCIÓN / INSTITUTION: - Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France, INSERM U900, Bioinformatique, biostatistique et epidemiologie d'un systeme complexe, Paris, France, Mines ParisTech, Fontainebleau, France, INSERM U830, Unite de Genetique et Biologie des Cancers, Paris, France and Institut Curie, Unite de genetique somatique, Paris, France.

RESUMEN / SUMMARY: - Ewing sarcoma is the second most frequent pediatric bone tumor. In most of the patients, a chromosomal translocation leads to the expression of the EWS-FLI1 chimeric transcription factor that is the major oncogene in this pathology. Relative genetic simplicity of Ewing sarcoma makes it particularly attractive for studying cancer in a systemic manner. Silencing EWS-FLI1 induces cell cycle alteration and ultimately leads to apoptosis, but the exact molecular mechanisms underlying this phenotype are unclear. In this study, a network linking EWS-FLI1 to cell cycle and apoptosis phenotypes was constructed through an original method of

network reconstruction. Transcriptome time-series after EWS-FLI1 silencing were used to identify core modulated genes by an original scoring method based on fitting expression profile dynamics curves. Literature data mining was then used to connect these modulated genes into a network. The validity of a subpart of this network was assessed by siRNA/RT-QPCR experiments on four additional Ewing cell lines and confirmed most of the links. Based on the network and the transcriptome data, CUL1 was identified as a new potential target of EWS-FLI1. Altogether, using an original methodology of data integration, we provide the first version of EWS-FLI1 network model of cell cycle and apoptosis regulation.

[291]

TÍTULO / TITLE: - Expression and prognostic significance of a comprehensive epithelial-mesenchymal transition gene set in renal cell carcinoma.

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

REVISTA / JOURNAL: - J Urol. 2013 Sep 4. pii: S0022-5347(13)05299-3. doi: 10.1016/j.juro.2013.08.052.

●● Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.08.052](#)

AUTORES / AUTHORS: - Chen D; Gassenmaier M; Maruschke M; Riesenberger R; Pohla H; Stief CG; Zimmermann W; Buchner A

INSTITUCIÓN / INSTITUTION: - Department of Urology, University Hospital, Ludwig-Maximilians-University, Munich, Germany; Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, China. Electronic address: dong.chen@med.uni-muenchen.de.

RESUMEN / SUMMARY: - PURPOSE: Epithelial-mesenchymal transition (EMT) enhances tumor cell motility and hence plays a critical role in invasion and metastasis in a number of carcinomas. A set of transcription factors act as master regulators of the EMT process. Whether EMT is important for tumor progression in clear cell renal cell carcinoma (RCC) is unknown. Therefore, we comprehensively assessed mRNA levels of EMT-associated genes in RCC and their prognostic relevance. MATERIALS AND METHODS: Expression of a set of 46 EMT-related genes was analyzed by oligonucleotide microarray and gene set enrichment analyses using RNA from normal kidney and G1 and G3 primary RCC, 14 samples each. Expression of selected EMT genes was validated by real-time polymerase chain reaction (PCR) in normal kidney, primary RCC and metastases in an independent cohort of 112 patients and then combined with follow-up data for survival analysis. RESULTS: The EMT gene set was preferentially expressed in primary RCC compared to normal tissue (false discovery rate 0.01), but no difference between G1 and G3 tumors was found. Quantitative RT-PCR showed down-regulation of critical EMT genes like CDH2 and ZEB1 in metastases which suggests reversal of EMT during metastasis. Kaplan-Meier analyses demonstrated a better outcome for patients with low CXCR4, vimentin, fibronectin and

TWIST1 mRNA levels. Multivariate analyses revealed that CXCR4 and vimentin up-regulation represents an independent prognostic marker for poor cancer-specific survival of RCC patients. CONCLUSIONS: Taken together, our data provide strong evidence that EMT occurs in RCC. Interference with EMT in RCC, therefore, might represent a future therapeutic option.

[292]

TÍTULO / TITLE: - High expression of small glutamine- rich tetratricopeptide repeat-containing protein alpha in esophageal squamous cell carcinoma correlates with proliferation and poor prognosis.

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

REVISTA / JOURNAL: - J Cell Biochem. 2013 Aug 12. doi: 10.1002/jcb.24641.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24641](#)

AUTORES / AUTHORS: - Yang X; Cheng L; Li M; Shi H; Ren H; Ding Z; Liu F; Wang Y; Cheng C

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Medical College, Nantong University, Nantong, Jiangsu, 226001, People's Republic of China; Department of Oncology, Affiliated Hospital of Nantong University, Nantong, Jiangsu, 226001, People's Republic of China.

RESUMEN / SUMMARY: - Receptor tyrosine kinases (RTKs) expression and the growth factor such as platelet-derived growth factor (PDGF) and their receptors have been considered relevant in the process of angiogenesis and dissemination in esophageal squamous cell carcinoma (ESCC). Small glutamine-rich tetratricopeptide repeat-containing protein alpha (SGTA) downstream of RTK signaling was a critical regulator of PDGF receptors (PDGFR) stability. The aim of the present study was to examine the expression of SGTA and to elucidate its clinicopathologic significance in ESCC. Immunohistochemistry and western blot analysis were performed for SGTA in ESCC samples. SGTA was up-regulated in ESCC as compared with the adjacent normal tissue. High expression of SGTA was associated with tumor grade ($P < 0.01$), and SGTA was positively correlated with proliferation marker Ki-67 ($P < 0.05$). Univariate analysis showed that SGTA expression did has a remarkable prediction for poor prognosis ($P = 0.016$). Knockdown or overexpression of SGTA affected ESCC cells proliferation and cell cycle. Additionally, after ESCC cells silenced for SGTA were treated with cisplatin (an anti-ESCC agent), the cell growth was down-regulated. These findings suggested that SGTA was involved in the pathogenesis of ESCC and might indicate a poor prognosis for ESCC patients. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[293]

TÍTULO / TITLE: - Sophoraflavanone G induces apoptosis of human cancer cells by targeting upstream signals of STATs.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Oct 1;86(7):950-9. doi: 10.1016/j.bcp.2013.08.009. Epub 2013 Aug 17.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.08.009](#)

AUTORES / AUTHORS: - Kim BH; Won C; Lee YH; Choi JS; Noh KH; Han S; Lee H; Lee CS; Lee DS; Ye SK; Kim MH

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Biomedical Science, Seoul National University College of Medicine, Seoul, Republic of Korea; Neuro-Immune Information Storage Network Research Center, Seoul National University College of Medicine, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - Aberrantly activated signal transducer and activator of transcription (STAT) proteins are implicated with human cancers and represent essential roles for cancer cell survival and proliferation. Therefore, the development of small-molecule inhibitors of STAT signaling bearing pharmacological activity has therapeutic potential for the treatment of human cancers. In this study, we identified sophoraflavanone G as a novel small-molecule inhibitor of STAT signaling in human cancer cells. Sophoraflavanone G inhibited tyrosine phosphorylation of STAT proteins in Hodgkin's lymphoma and tyrosine phosphorylation of STAT3 in solid cancer cells by inhibiting phosphorylation of the Janus kinase (JAK) proteins, Src family tyrosine kinases, such as Lyn and Src, Akt, and ERK1/2. In addition, sophoraflavanone G inhibited STAT5 phosphorylation in murine-bone-marrow-derived pro-B cells transfected with translocated Ets Leukemia (TEL)-JAKs and cytokine-induced rat pre-T lymphoma cells, as well as STAT5b reporter activity in TEL-JAKs and STAT5b reporter systems. Sophoraflavanone G also inhibited nuclear factor-kappaB (NF-kappaB) signaling in multiple myeloma cells. Furthermore, sophoraflavanone G inhibited cancer cell proliferation and induced apoptosis by regulating the expression of apoptotic and anti-apoptotic proteins. Our data suggest that sophoraflavanone G is a novel small-molecule inhibitor of STAT signaling by targeting upstream signals of STATs that may have therapeutic potential for cancers caused by persistently activated STAT proteins.

[294]

TÍTULO / TITLE: - Raddeanin A induces human gastric cancer cells apoptosis and inhibits their invasion in vitro.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 20;439(2):196-202. doi: 10.1016/j.bbrc.2013.08.060. Epub 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.08.060](#)

AUTORES / AUTHORS: - Xue G; Zou X; Zhou JY; Sun W; Wu J; Xu JL; Wang RP

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Nanjing University of Chinese Medicine, Nanjing, China.

RESUMEN / SUMMARY: - Raddeanin A is one of the triterpenoid saponins in herbal medicine *Anemone raddeana* Regel which was reported to suppress the growth of liver and lung cancer cells. However, little was known about its effect on gastric cancer (GC) cells. This study aimed to investigate its inhibitory effect on three kinds of different differentiation stage GC cells (BGC-823, SGC-7901 and MKN-28) in vitro and the possible mechanisms. Proliferation assay and flow cytometry demonstrated Raddeanin A's dose-dependent inhibitory effect and determined its induction of cells apoptosis, respectively. Transwell assay, wounding heal assay and cell matrix adhesion assay showed that Raddeanin A significantly inhibited the abilities of the invasion, migration and adhesion of the BGC-823 cells. Moreover, quantitative real time PCR and Western blot analysis found that Raddeanin A increased Bax expression while reduced Bcl-2, Bcl-xL and Survivin expressions and significantly activated caspase-3, caspase-8, caspase-9 and poly-ADP ribose polymerase (PARP). Besides, Raddeanin A could also up-regulate the expression of reversion inducing cysteine rich protein with Kazal motifs (RECK), E-cadherin (E-cad) and down-regulate the expression of matrix metalloproteinases-2 (MMP-2), MMP-9, MMP-14 and Rhoc. In conclusion, Raddeanin A inhibits proliferation of human GC cells, induces their apoptosis and inhibits the abilities of invasion, migration and adhesion, exhibiting potential to become antitumor drug.

[295]

TÍTULO / TITLE: - HOCl-dependent Singlet Oxygen and Hydroxyl Radical Generation Modulate and Induce Apoptosis of Malignant Cells.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3589-602.

AUTORES / AUTHORS: - Bauer G

INSTITUCIÓN / INSTITUTION: - Institut für Virologie, Department für Medizinische Mikrobiologie und Hygiene, Hermann-Herder Strasse 11, D-79104 Freiburg, Germany. georg.bauer@uniklinik-freiburg.de.

RESUMEN / SUMMARY: - The lack of extracellular superoxide anion production by non-transformed cells prevents H₂O₂/peroxidase-mediated HOCl synthesis by these cells, as well as apoptosis induction by exogenous HOCl. In contrast, transformed cells generate extracellular superoxide anions and HOCl, and die by apoptosis after HOCl/superoxide-dependent hydroxyl radical generation at their membrane. Tumor cells prevent HOCl synthesis through expression of membrane-associated catalase, but their extracellular superoxide anions readily react with exogenous HOCl. The interaction between HOCl and H₂O₂ causes singlet oxygen generation that inactivates superoxide dismutase (SOD) on the surface of the tumor cells and thus enhances HOCl-

mediated apoptosis through an increase in free superoxide anions. Higher concentrations of singlet oxygen inactivate membrane-associated catalase and thus lead to partial inhibition of apoptosis induction by exogenous HOCl, due to consumption of HOCl by H₂O₂. The data presented here show a complex, but coherent picture of interactions between defined reactive oxygen species and protective enzymes on the surface of tumor cells.

[296]

TÍTULO / TITLE: - N-acetyl-L-cysteine enhances fisetin-induced cytotoxicity via induction of ROS-independent apoptosis in human colonic cancer cells.

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

REVISTA / JOURNAL: - Mol Carcinog. 2013 Sep 9. doi: 10.1002/mc.22053.

●● Enlace al texto completo (gratis o de pago) [1002/mc.22053](#)

AUTORES / AUTHORS: - Wu MS; Lien GS; Shen SC; Yang LY; Chen YC

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; Division of Gastroenterology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.

RESUMEN / SUMMARY: - Oxidative stress or excessive antioxidant levels-caused redox imbalance can alter apoptotic responses, and N-acetyl-L-cysteine (NAC) was able to inhibit H₂O₂-mediated cell death, but unable to prevent apoptosis induced by other chemicals such as etoposide. We now demonstrate that 10 and 20 mM NAC, non-toxic concentrations, can enhance fisetin (FIS)-mediated apoptosis in colon cancer cells COLO205. Compared to treatment with FIS alone, combination treatment with NAC increased the expression of cleaved caspase-3 and PARP protein, and produced greater density of DNA ladders. NAC reduced the mitochondrial membrane potential of FIS-treated COLO205 cells with induction of caspase 9 protein cleavage. DNA ladders induced by FIS + NAC were diminished by adding the caspase 3 inhibitor, DEVD-FMK, and the caspase 9 inhibitor, YVAD-FMK. Combinatorial treatment COLO205 cells with NAC and FIS showed potent inhibition on ERK protein phosphorylation, compared with those from FIS or NAC-treated groups by Western blotting using specific antibodies. Addition of the chemical ERK inhibitors, PD98059 and U0126, significantly inhibited ERK protein phosphorylation, accompanied by induced DNA ladder formation, cleavage of caspase 3 and PARP protein in COLO205 cells. Furthermore, NAC showed an enhancement on a FIS-related chemical chrysin-induced apoptosis of COLO205 cells, and NAC sensitization of colon cancer cells to FIS-induced apoptosis was also identify in colonic cancer cells HCT-116, HT-29, and HCT-15 cells. The evidence to support NAC sensitizing human colon cancer cells to FIS-induced apoptosis was provided, and application of NAC and FIS as a strategy to treat colonic cancer deserved for further in vivo study. © 2013 Wiley Periodicals, Inc.

[297]

TÍTULO / TITLE: - Steroid receptor RNA activator protein (SRAP) expression as a prognostic factor in ER+ human breast tumors.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Oct;139(10):1637-47. doi: 10.1007/s00432-013-1485-2. Epub 2013 Aug 2.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00432-013-1485-2](#)

AUTORES / AUTHORS: - Yan Y; Penner CC; Skliris GP; Cooper C; Nugent Z; Blanchard A; Hamedani MK; Wang X; Myal Y; Murphy LC; Leygue E

INSTITUCIÓN / INSTITUTION: - Manitoba Institute of Cell Biology, 675 McDermot Ave., Winnipeg, MB, R3E0V9, Canada, umyan9@cc.umanitoba.ca.

RESUMEN / SUMMARY: - BACKGROUND: The steroid receptor RNA activator protein (SRAP) is a newly described protein modulating the activity of multiple transcription factors including the estrogen receptor (ER). We have recently reported the immunodetection by Western blot of multiple SRAP peptides in breast tissue. High expression of these peptides, assessed by tissue micro-array (TMA) analysis, was associated with poor prognosis in patients whose primary tumors were ER positive (ER+). In such studies, it is recognized that intensity as well as specificity of the signal detected directly depends upon the antibody used as well as the position of the epitope recognized. To confirm the potential relevance of SRAP as a new prognostic factor, it is critical to establish whether similar results are obtained with independent antibodies. METHODS: Two commercial anti-SRAP antibodies (742^a and 743^a), respectively, recognizing the N- and C-terminal extremity of the protein, were first used to analyze by Western blot SRAP expression in protein extracts from frozen breast tumor tissue sections. These antibodies were further used to investigate by immunohistochemistry (IHC) SRAP location in paraffin-embedded breast tumors. Comparative TMA analysis of 170 ER+ tumors was eventually performed in order to establish the potential associations existing between SRAP expression and clinical outcome. RESULTS: Multiple SRAP peptides were differentially detected by Western blot. Both antibodies led to similar nuclear and cytoplasmic staining in breast tissue section. A solid correlation was found (Spearman $r = 0.46$, $P < 0.001$) between 742^a and 743^a IHC scores. Results from both antibodies independently showed that dividing expression levels into lower 25 percentile, 26-75 percentile, and highest 25 percentile demonstrated a hazard ratio (HR) of 1.82 ($P = 0.0042$) for 742^a antibody and 1.35 ($P = 0.14$) for 743^a antibody. When both scores are combined, double high expressor (by 742^a and 743^a) was associated with a poor prognosis of breast-cancer-specific survival (Mantel-Cox: $P = 0.005$, $HR = 2.24$). CONCLUSION: Overall, our data suggest the existence in breast tumor tissue of multiple SRAP-like peptides. Assessing their expression in primary breast tumors can predict clinical outcome in ER+ breast cancer patients.

[298]

TÍTULO / TITLE: - Expression of HAb18G in non-small lung cancer and characterization of activation, migration, proliferation, and apoptosis in A549 cells following siRNA-induced downregulation of HAb18G.

RESUMEN / SUMMARY: -

ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24013786

●● Enlace al texto completo (gratis o de pago) 1007/s11010-013-1722-7

AUTORES / AUTHORS: - Xu X; Liu S; Lei B; Li W; Lin N; Sheng W; Huang A; Shen H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

RESUMEN / SUMMARY: - HAb18G, a novel cancer biomarker, has been shown to be involved in the progression of malignancy by regulating expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). The goal of this study was to evaluate the role of HAb18G in the biology of NSCLC and to determine its potential as a therapeutic target. HAb18G protein expression was detected by immunohistochemistry in 150 NSCLC tissues. The results showed that HAb18G protein expression was associated with tumor diameter, lymph node status, tumor stage, and poor prognosis ($P < 0.05$). Multivariate analysis showed that HAb18G overexpression was an independent prognostic factor (HR, 3.713; 95 % CI, 1.114-12.373; $P = 0.033$). Transient infection of A549 lung cancer cells with small interfering RNA (siRNA) against HAb18G efficiently inhibited the expression of HAb18G in A549 lung cancer cells at both mRNA and protein levels. Downregulation of HAb18G not only reduced MMP-2, MMP-9, and VEGF at mRNA and protein levels in A549 cells, but also inhibited fibroblasts to secrete MMP-2 and MMP-9 at mRNA level. Additionally, downregulation of HAb18G mRNA resulted in decreased migration, proliferation, and increased apoptosis of A549 in vitro. Our findings suggest that HAb18G overexpression plays an important role in progression of NSCLC and HAb18G may be a potential target of NSCLC therapy.

[299]

TÍTULO / TITLE: - The G-protein Coupled Receptor CLR is Up-regulated in an Autocrine Loop with Adrenomedullin in Clear Cell Renal Cell Carcinoma and Associated with Poor Prognosis.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) 1158/1078-0432.CCR-13-1712

AUTORES / AUTHORS: - Nikitenko LL; Leek R; Henderson S; Pillay N; Turley H; Generali D; Gunningham S; Morrin HR; Pellagatti A; Rees MC; Harris A; Fox SB

INSTITUCIÓN / INSTITUTION: - Viral Oncology Group, UCL Cancer Institute.

RESUMEN / SUMMARY: - PURPOSE: The G-protein coupled receptor (GPCR) CLR and its ligand peptide adrenomedullin (AM, encoded by ADM gene) are implicated in tumor angiogenesis in mouse models but poorly defined in human cancers. We therefore investigated the diagnostic/prognostic utility for CLR in human tumor types that may rely on AM signaling and in clear cell renal cell carcinoma (RCC), a highly vascular tumor, in particular. Experimental design: In silico gene expression messenger RNA profiling microarray study (n=168 tumors) and cancer profiling cDNA array hybridization (n=241 pairs of patient-matched tumor/normal tissue samples) were performed to analyze ADM mRNA expression in 13 tumor types. Immunohistochemistry on tissue microarrays containing patient-matched renal tumor/normal tissues (n=87 pairs) was performed to study CLR expression and its association with clinico-pathological parameters and disease outcome. RESULTS: ADM expression was significantly up-regulated only in RCC and endometrial adenocarcinoma compared with normal tissue counterparts (P<0.01). CLR was localized in tumor cells and vessels in RCC and up-regulated compared to patient-matched normal control kidney (P<0.001). Higher CLR expression was found in advanced stages (P<0.05), correlated with high tumor grade (P<0.01) and conferred shorter overall survival (P<0.01). CONCLUSIONS: In human tissues ADM expression is up-regulated in cancer-type specific manner, implicating potential role for AM signaling in particular in RCC, where CLR localization suggests autocrine/paracrine mode for AM action within the tumor microenvironment. Our findings reveal previously unrecognised CLR up-regulation in an autocrine loop with AM in RCC with potential application for this GPCR as a target for future functional studies and drug development.

[300]

TÍTULO / TITLE: - Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt277](#)

AUTORES / AUTHORS: - Abdel-Fatah TM; Perry C; Dickinson P; Ball G; Moseley P; Madhusudan S; Ellis IO; Chan SY

INSTITUCIÓN / INSTITUTION: - Clinical Oncology Department, Nottingham University Hospitals, Nottingham.

RESUMEN / SUMMARY: - BACKGROUND: TNBC represents a heterogeneous subgroup of BC with poor prognosis and frequently resistant to CT. MATERIAL AND METHODS: The relationship between Bcl2 immunohistochemical protein expression and clinico-

pathological outcomes was assessed in 736 TNBC-patients: 635 patients had early primary-TNBC (EP-TNBC) and 101 had primary locally advanced (PLA)-TNBC treated with neo-adjuvant- ATC-CT. RESULTS: Negative Bcl2 (Bcl2-) was observed in 70% of EP-TNBC and was significantly associated with high proliferation, high levels of P-Cadherin, E-Cadherin and HER3 (P's < 0.01), while Bcl2+ was significantly associated with high levels of p27, MDM4 and SPAG5 (P < 0.01). After controlling for chemotherapy and other prognostic factors, Bcl2- was associated with 2-fold increased risk of death (P = 0.006) and recurrence (P = 0.0004). Furthermore, the prognosis of EP-TNBC/Bcl2- patients had improved both BC-specific survival (P = 0.002) and disease-free survival (P = 0.003), if they received adjuvant-ATC-CT. Moreover, Bcl2- expression was an independent predictor of pathological complete response of primary locally advanced triple negative breast cancer (PLA-TNBC) treated with neoadjuvant-ATC-CT (P = 0.008). CONCLUSION: Adding Bcl2 to the panel of markers used in current clinical practice could provide both prognostic and predictive information in TNBC. TNBC/Bcl2- patients appear to benefit from ATC-CT, whereas Bcl2+ TNBC seems to be resistant to ATC-CT and may benefit from a trial of different type of chemotherapy with/without novel-targeted agents.

[301]

TÍTULO / TITLE: - Integration of cancer genomics with treatment selection: From the genome to predictive biomarkers.

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

REVISTA / JOURNAL: - Cancer. 2013 Aug 20. doi: 10.1002/cncr.28304.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28304](#)

AUTORES / AUTHORS: - Ow TJ; Sandulache VC; Skinner HD; Myers JN

INSTITUCIÓN / INSTITUTION: - Department of Otorhinolaryngology-Head and Neck Surgery, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York; Department of Pathology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York.

RESUMEN / SUMMARY: - The field of cancer genomics is rapidly advancing as new technology provides detailed genetic and epigenetic profiling of human cancers. The amount of new data available describing the genetic make-up of tumors is paralleled by rapid advances in drug discovery and molecular therapy currently under investigation to treat these diseases. This review summarizes the challenges and approaches associated with the integration of genomic data into the development of new biomarkers in the management of cancer. Cancer 2013. © 2013 American Cancer Society.

[302]

TÍTULO / TITLE: - Absence of FLICE-Inhibitory Protein Is a Novel Independent Prognostic Marker for Very Short Survival in Pancreatic Ductal Adenocarcinoma.

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

REVISTA / JOURNAL: - Pancreas. 2013 Oct;42(7):1114-9. doi: 10.1097/MPA.0b013e31829655ed.

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

[1097/MPA.0b013e31829655ed](#)

AUTORES / AUTHORS: - Schmid SJ; Glatzel MC; Welke C; Kornmann M; Kleger A; Barth TF; Fulda S; Lennerz JK; Moller P

INSTITUCIÓN / INSTITUTION: - From the *Department of Pathology, daggerComprehensive Cancer Center Ulm, and Departments of double daggerGeneral, Visceral and Transplantation Surgery and section signInternal Medicine, University Hospital Ulm, Germany; and parallelInstitute for Experimental Cancer Research in Pediatrics, Goethe-University Frankfurt, Germany.

RESUMEN / SUMMARY: - **OBJECTIVES:** Evading apoptosis is a hallmark of pancreatic cancer. In pancreatic cancer models, chemotherapy down-regulates the antiapoptotic protein cellular FLICE inhibitory protein (c-FLIP), which renders cells sensitive to apoptosis. Currently, the relevance of c-FLIP expression as a biomarker in pancreatic cancer is unknown, and here we assessed the prognostic significance of the c-FLIP expression status in a large cohort of pancreatic cancer patients with clinical follow-up. **METHODS:** Cellular FLICE inhibitory protein expression levels were determined by immunohistochemistry in 120 surgically resected ductal pancreatic adenocarcinomas. Survival analysis by c-FLIP status was compared with established clinicopathologic biomarkers as well as Ki-67 and cyclooxygenase 2 expression levels as 2 other established independent prognostic biomarkers in pancreatic cancer. **RESULTS:** Of 120 tumors, 111 (91%) were c-FLIP positive, whereas 9 (9%) were completely c-FLIP negative. Cyclooxygenase 2 was positive in 59 cases (52%), and Ki-67 was positive in more than 10% of tumor cells in 51 cases (44%). Univariate and multivariate survival analysis (correcting for stage, grade, and proliferation index) showed that c-FLIP is an independent prognostic factor. Specifically, c-FLIP negativity identifies 9% of patients with a highly aggressive disease course (P = 0.0001). **CONCLUSIONS:** Cellular FLICE inhibitory protein expression status is a valuable prognostic biomarker in pancreatic cancer.

[303]

TÍTULO / TITLE: - Apoptotic effect of methanol extract of *Picrasma quassioides* by regulating specificity protein 1 in human cervical cancer cells.

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

REVISTA / JOURNAL: - Cell Biochem Funct. 2013 Sep 13. doi: 10.1002/cbf.2996.

●● Enlace al texto completo (gratis o de pago) [1002/cbf.2996](#)

AUTORES / AUTHORS: - Lee HE; Choi ES; Shin JA; Kim LH; Cho NP; Cho SD

INSTITUCIÓN / INSTITUTION: - Department of Oral Pathology, School of Dentistry, Institute of Oral Bioscience, Chonbuk National University, Jeonju, Korea.

RESUMEN / SUMMARY: - In the present study, we examined the effects of methanol extracts of *Picrasma quassioides* (MEPQ) on apoptosis in human cervical cancer cells. The results showed that MEPQ decreased the viability and induced caspase-dependent apoptosis in HEP-2 cells. MEPQ decreased specificity protein 1 (Sp1) in HEP-2 cells, whereas Sp1 mRNA was not changed. We found that MEPQ reduced Sp1 protein through proteasome-dependent protein degradation, but not the inhibition of protein synthesis. Also, MEPQ increased the expressions of Bad and truncated Bid (t-Bid) but did not alter other Bcl-2 family members. The knock-down of Sp1 by both Sp1 interfering RNA and Mithramycin A, Sp1 specific inhibitor clearly increased Bad and t-Bid expression to decrease cell viability and induce apoptosis. In addition, MEPQ inhibited cell viability and induced apoptotic cell death through the modulation of Sp1 in KB cells. These results suggest that MEPQ may be a potential anticancer agent for human cervical cancer. Copyright © 2013 John Wiley & Sons, Ltd.

[304]

TÍTULO / TITLE: - Azathioprine desensitizes liver cancer cells to insulin-like growth factor 1 and causes apoptosis when it is combined with bafilomycin A1.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Aug 16;272(3):568-578. doi: 10.1016/j.taap.2013.07.024.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.07.024](https://doi.org/10.1016/j.taap.2013.07.024)

AUTORES / AUTHORS: - Hernandez-Breijo B; Monserrat J; Roman ID; Gonzalez-Rodriguez A; Fernandez-Moreno MD; Lobo MV; Valverde AM; Gisbert JP; Guijarro LG

INSTITUCIÓN / INSTITUTION: - Departamento de Biología de Sistemas, Centro de Investigación Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBEREHD), Universidad de Alcalá, 28871 Alcalá de Henares, España.

RESUMEN / SUMMARY: - Hepatoblastoma is a primary liver cancer that affects children, due to the sensitivity of this tumor to insulin-like growth factor 1 (IGF-1). In this paper we show that azathioprine (AZA) is capable of inhibiting IGF1-mediated signaling cascade in HepG2 cells. The efficiency of AZA on inhibition of proliferation differs in the evaluated cell lines as follows: HepG2 (an experimental model of hepatoblastoma)>Hep3B (derived from a hepatocellular carcinoma)>HuH6 (derived from a hepatoblastoma)>>HuH7 (derived from a hepatocellular carcinoma)=Chang Liver cells (a non-malignant cellular model). The effect of AZA in HepG2 cells has been proven to derive from activation of Ras/ERK/TSC2, leading to activation of mTOR/p70S6K in a sustained manner. p70S6K phosphorylates IRS-1 in serine 307 which leads to the uncoupling between IRS-1 and p85 (the regulatory subunit of PI3K)

and therefore causing the lack of response of HepG2 to IGF-1. As a consequence, proliferation induced by IGF-1 is inhibited by AZA and autophagy increases leading to senescence of HepG2 cells. Our results suggest that AZA induces the autophagic process in HepG2 activating senescence, and driving to deceleration of cell cycle but not to apoptosis. However, when simultaneous to AZA treatment the autophagy was inhibited by bafilomycin A1 and the degradation of regulatory proteins of cell cycle (e.g. Rb, E2F, and cyclin D1) provoked apoptosis. In conclusion, AZA induces resistance in hepatoblastoma cells to IGF-1, which leads to autophagy activation, and causes apoptosis when it is combined with bafilomycin A1. We are presenting here a novel mechanism of action of azathioprine, which could be useful in treatment of IGF-1 dependent tumors, especially in its combination with other drugs.

[305]

TÍTULO / TITLE: - Valproic Acid Sensitizes TRAIL-Resistant Anaplastic Thyroid Carcinoma Cells to Apoptotic Cell Death.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3232-y](#)

AUTORES / AUTHORS: - Cha HY; Lee BS; Kang S; Shin YS; Chang JW; Sung ES; Kim YS; Choi JW; Kim JH; Kim CH

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology, School of Medicine, Ajou University, Suwon, Korea.

RESUMEN / SUMMARY: - BACKGROUND: Anaplastic thyroid carcinoma (ATC) is an aggressive human tumor associated with a median survival of 2-6 months. TRAIL, as a ligand of death receptors, is known to induce apoptotic cell death in several cancer cells. However, TRAIL treatment alone is not effective against TRAIL-resistant cancer cells. This study was designed to investigate whether valproic acid (VPA) enhances apoptotic cell death of TRAIL-resistant ATC cells and to identify the mechanism of cell death of ATC cells by combination treatment with VPA and TRAIL. METHODS: To evaluate the cytotoxic effect of TRAIL and/or VPA on ATC cells, we used the MTT assay. The effects of VPA and TRAIL on apoptosis were assessed using FACS analysis (Annexin-V/PI stain) and Western blotting. RESULTS: The combination of VPA with TRAIL significantly induced apoptotic cell death compared with 8505C and ARO cells treated with TRAIL alone. The protein levels of cleaved caspase-8, -3, and PARP were increased in VPA and TRAIL co-treated ARO cells. The combination induced the activation of JNK and the phosphorylation of FADD and c-Jun but not p38. However, pretreatment with caspase inhibitors reduced the expression of cleaved caspase-8, -3, and PARP in co-treated ARO cells. SP600125 remarkably reduced the expression of cleaved caspase-8, -3, and PARP and the phosphorylation of FADD and c-Jun, as well as apoptotic cell death. CONCLUSIONS: VPA sensitized TRAIL-resistant ATC cells to

apoptotic cell death through involvement of the JNK pathway. Thus, the combination of VPA and TRAIL may be a promising therapy for ATC.

[306]

TÍTULO / TITLE: - Survival in stage II/III colorectal cancer is independently predicted by chromosomal and microsatellite instability, but not by specific driver mutations.

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

REVISTA / JOURNAL: - Am J Gastroenterol. 2013 Sep 17. doi: 10.1038/ajg.2013.292.

●● [Enlace al texto completo \(gratis o de pago\) 1038/ajg.2013.292](#)

AUTORES / AUTHORS: - Mouradov D; Domingo E; Gibbs P; Jorissen RN; Li S; Soo PY; Lipton L; Desai J; Danielsen HE; Oukrif D; Novelli M; Yau C; Holmes CC; Jones IT; McLaughlin S; Molloy P; Hawkins NJ; Ward R; Midgely R; Kerr D; Tomlinson IP; Sieber OM

INSTITUCIÓN / INSTITUTION: - 1] Ludwig Colon Cancer Initiative Laboratory, Ludwig Institute for Cancer Research, Parkville, Victoria, Australia [2] Faculty of Medicine, Dentistry and Health Sciences, Department of Medical Biology, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia.

RESUMEN / SUMMARY: - OBJECTIVES:Microsatellite instability (MSI) is an established marker of good prognosis in colorectal cancer (CRC). Chromosomal instability (CIN) is strongly negatively associated with MSI and has been shown to be a marker of poor prognosis in a small number of studies. However, a substantial group of “double-negative” (MSI-/CIN-) CRCs exists. The prognosis of these patients is unclear. Furthermore, MSI and CIN are each associated with specific molecular changes, such as mutations in KRAS and BRAF, that have been associated with prognosis. It is not known which of MSI, CIN, and the specific gene mutations are primary predictors of survival.METHODS:We evaluated the prognostic value (disease-free survival, DFS) of CIN, MSI, mutations in KRAS, NRAS, BRAF, PIK3CA, FBXW7, and TP53, and chromosome 18q loss-of-heterozygosity (LOH) in 822 patients from the VICTOR trial of stage II/III CRC. We followed up promising associations in an Australian community-based cohort (N=375).RESULTS:In the VICTOR patients, no specific mutation was associated with DFS, but individually MSI and CIN showed significant associations after adjusting for stage, age, gender, tumor location, and therapy. A combined analysis of the VICTOR and community-based cohorts showed that MSI and CIN were independent predictors of DFS (for MSI, hazard ratio (HR)=0.58, 95% confidence interval (CI) 0.36-0.93, and P=0.021; for CIN, HR=1.54, 95% CI 1.14-2.08, and P=0.005), and joint CIN/MSI testing significantly improved the prognostic prediction of MSI alone (P=0.028). Higher levels of CIN were monotonically associated with progressively poorer DFS, and a semi-quantitative measure of CIN was a better predictor of outcome than a simple CIN+/- variable. All measures of CIN predicted DFS better than the recently described Watanabe LOH ratio.CONCLUSIONS:MSI and CIN are independent

predictors of DFS for stage II/III CRC. Prognostic molecular tests for CRC relapse should currently use MSI and a quantitative measure of CIN rather than specific gene mutations. Am J Gastroenterol advance online publication, 17 September 2013; doi:10.1038/ajg.2013.292.

[307]

TÍTULO / TITLE: - Protein kinase inhibitor gamma reciprocally regulates osteoblast and adipocyte differentiation by downregulating leukemia inhibitory factor.

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

REVISTA / JOURNAL: - Stem Cells. 2013 Aug 20. doi: 10.1002/stem.1524.

●● Enlace al texto completo (gratis o de pago) [1002/stem.1524](#)

AUTORES / AUTHORS: - Chen X; Hausman BS; Luo G; Zhou G; Murakami S; Rubin J; Greenfield EM

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106.

RESUMEN / SUMMARY: - The Protein Kinase Inhibitor (Pki) gene family inactivates nuclear PKA and terminates PKA-induced gene expression. We previously showed that Pkiγ is the primary family member expressed in osteoblasts and that Pkiγ knockdown increases the effects of parathyroid hormone and isoproterenol on PKA activation, gene expression, and inhibition of apoptosis. Here, we determined whether endogenous levels of Pkiγ regulate osteoblast differentiation. Pkiγ is the primary family member in MEFs, murine marrow-derived mesenchymal stem cells, and human mesenchymal stem cells. Pkiγ deletion increased forskolin-dependent nuclear PKA activation and gene expression and Pkiγ deletion or knockdown increased osteoblast differentiation. PKA signaling is known to stimulate adipogenesis; however, adipogenesis and osteogenesis are often reciprocally regulated. We found that the reciprocal regulation predominates over the direct effects of PKA since adipogenesis was decreased by Pkiγ deletion or knockdown. Pkiγ deletion or knockdown simultaneously increased osteogenesis and decreased adipogenesis in mixed osteogenic/adipogenic medium. Pkiγ deletion increased PKA-induced expression of Leukemia Inhibitory Factor (Lif) mRNA and LIF protein. LIF neutralizing antibodies inhibited the effects on osteogenesis and adipogenesis of either Pkiγ deletion in MEFs or Pkiγ knockdown in both murine and human mesenchymal stem cells. Collectively, our results show that endogenous levels of Pkiγ reciprocally regulate osteoblast and adipocyte differentiation and that this reciprocal regulation is mediated in part by LIF. Stem Cells 2013.

[308]

TÍTULO / TITLE: - Proteasome inhibitor MG132 enhances TRAIL-induced apoptosis and inhibits invasion of human osteosarcoma OS732 cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 20;439(2):179-86. doi: 10.1016/j.bbrc.2013.08.066. Epub 2013 Aug 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.08.066](#)

AUTORES / AUTHORS: - Li X; Huang T; Jiang G; Gong W; Qian H; Zou C

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, The First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning, PR China.

RESUMEN / SUMMARY: - MG132 as a proteasome inhibitor could induce apoptosis in various cancer cells. This study aimed to discuss the effect of proteasome inhibitor MG132 on the TRAIL-induced apoptosis of human osteosarcoma OS732 cells. MG132 and TRAIL were applied on OS732 cells respectively or jointly. Cell survival rates, changes of cellular shape, cell apoptosis and cell invasion were analyzed, respectively, by 3-(4,5)-dimethylthiazol-2,5-diphenyltetrazolium bromide (MTT) assay, inverted phase contrast microscope, flow cytometry, and transwell invasion chamber methods. The protein levels of DR5, caspase-3, caspase-8, p27(kip1) and MMP-9 were measured by Western blot analysis. The results indicated that combination of MG132 and TRAIL had the effect of up-regulating expression of DR5, caspase-3, caspase-8 and p27(kip1), down-regulating expression of MMP-9 and inducing apoptosis as well as suppressing the ability of invasion of OS732 cells. The survival rate of combined application of 10µM MG132 and 100ng/ml TRAIL on OS732 cells was significantly lower than that of the individual application ($p < 0.01$). Changes of cellular shape and apoptotic rates also indicated the apoptosis-inducing effect of combined application was much stronger than that of individual application. Cell cycle analysis showed combination of MG132 and TRAIL mostly caused OS732 cells arrested at G2-M-phase. The invasion ability of OS732 cells was restrained significantly in the combined group compared with the individual group and control group.

[309]

TÍTULO / TITLE: - gamma-Glutamyl hydrolase modulation and folate influence chemosensitivity of cancer cells to 5-fluorouracil and methotrexate.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17. doi: 10.1038/bjc.2013.579.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.579](#)

AUTORES / AUTHORS: - Kim SE; Cole PD; Cho RC; Ly A; Ishiguro L; Sohn KJ; Croxford R; Kamen BA; Kim YI

INSTITUCIÓN / INSTITUTION: - [1] Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada M5S 1A8 [2] Keenan Research Center, Li Ka Shing Knowledge Institute at St. Michael's Hospital, Toronto, Ontario, Canada M5B 1W8.

RESUMEN / SUMMARY: - Background:gamma-Glutamyl hydrolase (GGH) regulates intracellular folate and antifolates for optimal nucleotide biosynthesis and antifolate-induced cytotoxicity, respectively. The modulation of GGH may therefore affect chemosensitivity of cancer cells, and exogenous folate levels may further modify this effect.Methods:We generated a novel model of GGH modulation in human HCT116 and MDA-MB-435 cancer cells and investigated the effect of GGH modulation on chemosensitivity to 5-fluorouracil (5FU) and methotrexate (MTX) at different folate concentrations in vitro and in vivo.Results:Overexpression of GGH significantly decreased chemosensitivity of MDA-MB-435 cells to 5FU and MTX at all folate concentrations as expected. In contrast, in HCT116 cells this predicted effect was observed only at very high folate concentration, and as the folate concentration decreased this effect became null or paradoxically increased. This in vitro observation was confirmed in vivo. Inhibition of GGH significantly increased chemosensitivity of both cancer cells to 5FU at all folate concentrations. Unexpectedly, GGH inhibition significantly decreased chemosensitivity of both cancer cells to MTX at all folate concentrations. In both GGH modulation systems and cell lines, the magnitude of chemosensitivity effect incrementally increased as folate concentration increased.Conclusion:Modulation of GGH affects chemosensitivity of cancer cells to 5FU and MTX, and exogenous folate levels can further modify the effects.British Journal of Cancer advance online publication, 17 September 2013; doi:10.1038/bjc.2013.579 www.bjcancer.com.

[310]

TÍTULO / TITLE: - BMP4 is Involved in the Chemoresistance of Myeloid Leukemia Cells Through Regulating Autophagy-Apoptosis Balance.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Oct;31(8):555-562. Epub 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.834925](https://doi.org/10.1007/s12094-013-8349-2)

AUTORES / AUTHORS: - Zhao X; Liu J; Peng M; Liu J; Chen F

INSTITUCIÓN / INSTITUTION: - 1Department of Hematology, Xiangya Hospital.

RESUMEN / SUMMARY: - This study showed that silencing BMP4 expression significantly activated caspase-2, 3, and 9, while decreasing Matrigel colony formation in Cytarabine (Ara-C)-treated leukemia HL-60 cells. In contrast, Ara-C significantly upregulated Atg5 and Beclin-1 expression, the ratio of LC3-II/LC3-I, and CDK1 and cyclin B1 expression in leukemia cells expressing BMP4. BafA significantly sensitized the apoptotic effect of Ara-C in leukemia cells. Injection of Ara-C significantly inhibited tumor growth in mice inoculated with leukemia cells with BMP4 silenced. In conclusion, BMP4 plays a crucial role in the chemoresistance of leukemia cells through the activation of autophagy and subsequent inhibition of apoptosis.

[311]

TÍTULO / TITLE: - Increased expression of Slug and Vimentin as novel predictive biomarkers for lymph node metastasis and poor prognosis in colorectal cancer.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Sep 24.

- Enlace al texto completo (gratis o de pago) [1093/carcin/bgt282](#)

AUTORES / AUTHORS: - Toiyama Y; Yasuda H; Saigusa S; Tanaka K; Inoue Y; Goel A; Kusunoki M

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Mie University Graduate School of Medicine, Mie 514-8507, Japan and.

RESUMEN / SUMMARY: - Slug and Vimentin genes play a critical role in regulating epithelial-mesenchymal transition (EMT) via downregulation of epithelial markers and upregulation of mesenchymal markers. The present study evaluated the clinical significance of Slug and Vimentin expression as potential disease biomarkers in colorectal cancer (CRC). At first, the biological role of Slug in CRC was assessed by RNA interference in CRC cell lines to assess tumor progression, invasion and migration. Next, we analyzed Slug and Vimentin expression in surgical tissue specimens from 181 CRC patients (Cohort 1) by quantitative real-time reverse transcription-PCR and 208 patients (Cohort 2) by immunohistochemistry. Knockdown of Slug using small interfering RNA in CRC cell lines resulted in inhibition of EMT, reduced cell proliferation, invasion and migration in CRC cells. Interestingly, Slug and Vimentin expression in cancer tissues was significantly higher in patients with higher T stage, lymph node involvement, liver metastasis and advanced tumor node metastasis stages. A significant correlation was observed between Slug and Vimentin expression in CRC (messenger RNA: $\rho = 0.546$, protein: $\rho = 0.405$), and increased expression of Slug and Vimentin was significantly associated with poor prognosis. Furthermore, increased expression of Slug emerged as an independent prognostic factor and a predictive marker of lymph node metastasis in CRC patients. Our data provide novel evidence for the biological and clinical significance of Slug and Vimentin expression as potential predictive biomarkers for identifying patients with lymph node metastasis or poor prognosis in CRC.

[312]

TÍTULO / TITLE: - Aberrant Expression miR-196^a Is Associated With Abnormal Apoptosis, Invasion, and Proliferation of Pancreatic Cancer Cells.

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

REVISTA / JOURNAL: - Pancreas. 2013 Oct;42(7):1169-81. doi: 10.1097/MPA.0b013e3182962acb.

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

[1097/MPA.0b013e3182962acb](https://doi.org/10.1097/MPA.0b013e3182962acb)

AUTORES / AUTHORS: - Liu M; Du Y; Gao J; Liu J; Kong X; Gong Y; Li Z; Wu H; Chen H

INSTITUCIÓN / INSTITUTION: - From the Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - OBJECTIVES: MiR-196^a levels inversely correlated with survival in pancreatic adenocarcinoma patients. However, the functional contributions of miR-196^a to pancreatic cancer remain unclear. METHODS: Three lentiviral vectors encoding microRNA miR-196^a precursor, inhibitor, and scrambled microRNA oligomer were transfected into Panc-1 cells, respectively. Then we explored the regulation of inhibitor of growth 5 (ING5) expression by miR-196^a and its impact on apoptosis, invasion, and growth of pancreatic cancer cells. The lentiviral transfected Panc-1 cells were surgically implanted into the pancreas of mice. In vivo tumor growth and ING5 expression were measured. RESULTS: Down-regulation of ING5 expression was detected in cells transfected with miR-196^a precursor (P < 0.01), accompanied by less apoptosis, increased invasion, and proliferation compared with control cells (P < 0.05). Cells transfected with miR-196^a inhibitor revealed an opposite trend. Smaller detectable tumors were found in only 60% of mice after implantation of Lenti.miR-196^a inhibitor-transfected Panc-1 cells compared with controls (360.7 +/- 303.6 mm vs 511.58 +/- 365.9 mm in controls; P < 0.01). CONCLUSION: Our results provide experimental evidence to support aberrant expression of miR-196^a is associated with abnormal apoptosis, invasion, and proliferation of pancreatic cancer cells.

[313]

TÍTULO / TITLE: - Modulation of the expression of folate cycle enzymes and polyamine metabolism by berberine in cisplatin-sensitive and -resistant human ovarian cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1269-80. doi: 10.3892/ijo.2013.2045. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2045](https://doi.org/10.3892/ijo.2013.2045)

AUTORES / AUTHORS: - Marverti G; Ligabue A; Lombardi P; Ferrari S; Monti MG; Frassinetti C; Costi MP

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, Metabolic and Neuroscience, Section of Pharmacology and Molecular Medicine, University of Modena and Reggio Emilia, I-41125 Modena, Italy.

RESUMEN / SUMMARY: - Berberine is a natural isoquinoline alkaloid with significant antitumor activity against many types of cancer cells, including ovarian tumors. This study investigated the molecular mechanisms by which berberine differently affects cell growth of cisplatin (cDDP)-sensitive and -resistant and polyamine analogue cross-

resistant human ovarian cancer cells. The results show that berberine suppresses the growth of cDDP-resistant cells more than the sensitive counterparts, by interfering with the expression of folate cycle enzymes, dihydrofolate reductase (DHFR) and thymidylate synthase (TS). In addition, the impairment of the folate cycle also seems partly ascribable to a reduced accumulation of folate, a vitamin which plays an essential role in the biosynthesis of nucleic acids and amino acids. This effect was observed in both lines, but especially in the resistant cells, correlating again with the reduced tolerance to this isoquinoline alkaloid. The data also indicate that berberine inhibits cellular growth by affecting polyamine metabolism, in particular through the upregulation of the key catabolic enzyme, spermidine/spermine N1-acetyltransferase (SSAT). In this regard, berberine is shown to stimulate the SSAT induction by the spermine analogue N1, N12 bisethylspermine (BESpm), which alone was also able to downregulate DHFR mRNA more than TS mRNA. We report that the sensitivity of resistant cells to cisplatin or to BESpm is reverted to the levels of sensitive cells by the co-treatment with berberine. These data confirm the intimate inter-relationships between folate cycle and polyamine pathways and suggest that this isoquinoline plant alkaloid could be a useful adjuvant therapeutic agent in the treatment of ovarian carcinoma.

[314]

TÍTULO / TITLE: - Antidepressants attenuate the dexamethasone-induced decrease in viability and proliferation of human neuroblastoma SH-SY5Y cells: A involvement of extracellular regulated kinase (ERK1/2).

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

REVISTA / JOURNAL: - Neurochem Int. 2013 Jul 29;63(5):354-362. doi: 10.1016/j.neuint.2013.07.007.

●● Enlace al texto completo (gratis o de pago) 1016/j.neuint.2013.07.007

AUTORES / AUTHORS: - Leskiewicz M; Jantas D; Regulska M; Kaczanowska J; Basta-Kaim A; Budziszewska B; Kubera M; Lason W

INSTITUCIÓN / INSTITUTION: - Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Krakow, Poland.

RESUMEN / SUMMARY: - Excessive glucocorticoid levels in depressed patients have been associated with atrophic changes in some brain regions, but only few studies suggest that some antidepressants can interfere with deleterious effect of glucocorticoids on neuronal cells. The aim of the present study was to examine the effect of dexamethasone (DEX), a synthetic glucocorticoid and some antidepressants from different chemical groups (imipramine, desipramine, amitriptyline, citalopram, fluoxetine, reboxetine and tianeptine) on SH-SY5Y cells cultured in the medium containing steroid-free serum. DEX in concentrations from 1 to 100µM did not change LDH release but exposure to 10µM and 100µM DEX for 24, 48 and 72h

caused a significant reduction in cell viability and proliferation as confirmed by MTT reduction and BrdU ELISA assays, respectively. Twenty four-hour incubation of cells with antidepressants (0.05-10µM) and DEX (10µM) showed that imipramine, amitriptyline, desipramine, citalopram and fluoxetine at concentrations from 0.1 up to 1µM, reboxetine (0.1µM) and tianeptine (0.05µM) prevented the DEX-induced decreases in cell viability and proliferation rate. The protective effects of antidepressants were ameliorated by inhibitors of MAPK/ERK1/2, but not PI3-K/Akt pathway as shown for imipramine, fluoxetine and reboxetine. Moreover, Western blot analysis showed the decrease in the activated form of ERK1/2 (p-ERK) after DEX treatment and this effect was inhibited by imipramine. Thus, the reduction in SH-SY5Y cell viability caused by DEX appears to be related to its antiproliferative activity and some antidepressant drugs in low concentrations attenuate this effect by mechanism which involves the activation of MAPK/ERK1/2 pathway.

[315]

TÍTULO / TITLE: - Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation.

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

REVISTA / JOURNAL: - Neurology. 2013 Sep 25.

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

[1212/WNL.0b013e3182a95680](#)

AUTORES / AUTHORS: - Wick W; Meisner C; Hentschel B; Platten M; Schilling A; Wiestler B; Sabel MC; Koepfen S; Ketter R; Weiler M; Tabatabai G; von Deimling A; Gramatzki D; Westphal M; Schackert G; Loeffler M; Simon M; Reifenberger G; Weller M

INSTITUCIÓN / INSTITUTION: - From the Departments of Neuro-oncology (W.W., M.P., A.S., B.W., M. Weiler) and Neuropathology (A.v.D.), University of Heidelberg; German Cancer Consortium (DKTK) (W.W., B.W., M. Weiler), Clinical Cooperation Unit Neuro-oncology and Clinical Cooperation Unit Neuropathology (A.v.D.), German Cancer Research Center, Heidelberg; Department of Medical Biometry (C.M.), University of Tübingen; Institute for Medical Informatics, Statistics and Epidemiology (B.H., M.L.), University Leipzig; Departments of Neurosurgery (M.C.S.) and Neuropathology (G.R.), Heinrich-Heine-University and DKTK (G.R.), Düsseldorf; Department of Neurology (S.K.), University of Essen Medical School; Department of Neurosurgery (R.K.), Saarland University, Homburg, Germany; Department of Neurology (G.T., D.G., M. Weller), University Hospital Zurich, Switzerland; Department of Neurosurgery (M. Westphal), University Clinic Hamburg Eppendorf, Hamburg; Department of Neurosurgery (G.S.) and DKTK (G.S.), Technical University Dresden; and Department of Neurosurgery (M.S.), University of Bonn, Germany.

RESUMEN / SUMMARY: - OBJECTIVE: To explore whether the isocitrate dehydrogenase 1 (IDH1) or 1p/19q status determines the prognostic vs predictive role of O6-

methylguanine-DNA methyltransferase (MGMT) promoter methylation in the Neuro-Oncology Working Group of the German Cancer Society (NOA)-04 trial anaplastic glioma biomarker cohort. METHODS: Patients (n = 183) of the NOA-04 trial with known MGMT and IDH1 status were analyzed for interdependency of the prognostic vs predictive role of MGMT promoter methylation from IDH1 or 1p/19q status and treatment, using progression-free survival (PFS) as an endpoint. An independent validation cohort of the German Glioma Network (n = 75) and the NOA-08 trial (n = 34) served as a confirmation cohort. RESULTS: In tumors with IDH1 mutation, MGMT promoter methylation was associated with prolonged PFS with chemotherapy +/- radiotherapy (RT) or RT-only groups, and is thus prognostic. In tumors without IDH1 mutation, MGMT promoter methylation was associated with increased PFS in patients treated with chemotherapy, but not in those who received RT alone as the first-line treatment, and is thus chemotherapy-predictive. In contrast, 1p/19q codeletions showed no such association with the prognostic vs predictive value of MGMT. CONCLUSIONS: MGMT promoter methylation is a predictive biomarker for benefit from alkylating agent chemotherapy in patients with IDH1-wild-type, but not IDH1-mutant, malignant gliomas of World Health Organization grades III/IV. Combined IDH1/MGMT assessment may help to individualize clinical decision-making in neuro-oncology.

[316]

TÍTULO / TITLE: - Prostate-Specific Antigen Velocity Risk Count Predicts Biopsy Reclassification for Men with Very-Low-Risk Prostate Cancer.

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

REVISTA / JOURNAL: - J Urol. 2013 Sep 20. pii: S0022-5347(13)05468-2. doi: 10.1016/j.juro.2013.09.029.

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

AUTORES / AUTHORS: - Patel HD; Feng Z; Landis P; Trock BJ; Epstein JI; Carter HB

INSTITUCIÓN / INSTITUTION: - James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD. Electronic address: hitenpatel@jhmi.edu.

RESUMEN / SUMMARY: - PURPOSE: Prostate-specific antigen velocity (PSAV) has been found to be an unreliable predictor of adverse pathology for patients on active surveillance for low-risk prostate cancer. However, a new concept called PSAV risk count (RC), recently validated in a screening cohort, has not been investigated in an active surveillance cohort. MATERIALS AND METHODS: We evaluated a cohort of men (1995-2012) with prostate cancer on active surveillance (stage T1c disease, PSA density <0.15 ng/mL, Gleason score ≤6, ≤2 biopsy cores and ≤50% involvement of any core with cancer). Men were observed by semiannual PSA measurements, digital rectal examinations, and an annual surveillance biopsy. Treatment was recommended for biopsy reclassification. Patients with ≥30 months follow-up and three serial

PSAVs constituted the primary analysis using logistic regression, Cox proportional hazards, Kaplan-Meier analysis, and performance parameters including area under the receiver operating characteristic curve (AUC). RESULTS: Primary analysis included 275 of 668 men meeting very-low-risk inclusion criteria with 83(30.2%) reclassified at 57.1 months (median). Reclassification risk increased with RC with associations for a RC of three [HR4.63 (95%CI 1.54-13.87)] and two [HR3.73 (95%CI 1.75-7.97)] compared to zero, and similarly for Gleason score reclassification (RC of three [HR7.45 (95%CI 1.60-34.71)] and two [HR3.96 (95%CI 1.35-11.62)]). Negative predictive value (RC \leq 1) was 91.5% for reclassification in the next year on secondary analysis. Addition of PSAV RC improved AUC for a model including baseline PSA density (0.7423vs.0.6818,p=0.025) and outperformed addition of overall PSAV (0.7423vs.0.6960,p=0.037). CONCLUSION: PSAV RC may be useful to monitor patients on active surveillance and reduce the frequency of biopsies needed in the long-term.

[317]

TÍTULO / TITLE: - A DNA vaccine against cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) prevents tumor growth.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 13. pii: S0006-291X(13)01502-7. doi: 10.1016/j.bbrc.2013.09.031.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.09.031

AUTORES / AUTHORS: - Lan KH; Liu YC; Shih YS; Yen SH; Lan KL

INSTITUCIÓN / INSTITUTION: - Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei 100, Taiwan.

RESUMEN / SUMMARY: - Co-stimulatory signaling pathway triggered by the binding of B7.1/B7.2 (CD80/86) of antigen-presenting cells (APCs) to CD28 of T cells is required for optimal T-cell activation. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is a negative regulator of T cell activation, which competes with CD28 for B7.1/B7.2 binding with a greater affinity. Ipilimumab, a monoclonal antibody against CTLA-4, has shown positive efficacy in a pivotal clinical trial for the treatment of metastatic melanoma and was approved by FDA. However, the cost of monoclonal antibody-based therapeutics might limit the number of patients treated. To develop a novel therapeutics specifically targeting CTLA-4, we constructed a DNA vaccine by cloning the sequence of CTLA-4 fused with a transmembrane domain sequence of placental alkaline phosphatase (PLAP) into a mammalian expression plasmid, pVAC-1. Immunization with the resulting construct, pVAC-1-hCTLA-4, elicited antibody specific to human CTLA-4 with cross reactivity to murine CTLA-4, which was sufficient for inhibiting B16F10 tumor growth in c57BL/6 mice in the absence of measurable toxicity. Coupling liposome with pVAC-1-mCTLA-4 could break tolerance to self-antigen in

BALB/c mice and induce potent immunity against murine CTLA-4, and suppress growth of subcutaneous renal cell carcinoma (Renca).

[318]

TÍTULO / TITLE: - The role of epithelial-mesenchymal transition and IGF-1R expression in prediction of gefitinib activity as the second-line treatment for advanced nonsmall-cell lung cancer.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Aug;31(7):454-60. doi: 10.3109/07357907.2013.820315.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.820315](#)

AUTORES / AUTHORS: - Chen B; Xiao F; Li B; Xie B; Zhou J; Zheng J; Zhang W

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, Guangdong, P. R. China.

RESUMEN / SUMMARY: - OBJECTIVE: Except for EGFR gene mutation, there is still lack of predictive factors for gefitinib activity as the second-line treatments for advanced NSCLC with wild-type (WT) EGFR or patients with mutant EGFR but showed poor response. Our purpose was to assess the predictive value of epithelial-mesenchymal transition (EMT) and IGF-1R for gefitinib efficacy as the second-line treatment for NSCLC. METHODS: 53 advanced NSCLC patients who accepted gefitinib as the second-line treatment were enrolled in this study. Expression of E-cadherin, vimentin, and IGF-1R was determined by immunohistochemistry. EGFR gene mutation was determined by liquidchip technique. RESULTS: The positive rate of EMT, IGF-1R, and EGFR gene mutation was 54.7%, 58.5%, and 39.6%, respectively. EMT (-) was positively correlated with EGFR gene mutation ($p = .034$) and EMT (+) was associated with IGF-1R (+) ($p = .000$). EMT (-) was associated with a significantly higher objective response rate (ORR) for all the 53 patients (41.7% vs. 6.9%, $p = .024$) and showed a higher ORR tendency than EMT (+) in EGFR mutation patients (50.0% vs. 28.6%) and WT EGFR patients (20.0% vs. 4.5%) ($p > .05$). EMT (-) showed a significant longer median survival time (MST) than EMT (+) for all 53 patients (8 months vs. 4 months) and WT EGFR patients (6 months vs. 3 months) ($p < .05$). IGF-1R (-) showed a higher ORR tendency than IGF-1R (+) in EGFR mutation patients (54% vs. 30%) and WT EGFR patients (18.2% vs. 4.8%) ($p > .05$). CONCLUSION: EMT is correlated with efficacy of gefitinib as the second-line treatment for NSCLC, and combined detection of EMT and IGF-1R may be used as new predictors besides EGFR mutation, especially for patients with WT EGFR.

[319]

TÍTULO / TITLE: - Curcumin suppresses proliferation and induces apoptosis of human hepatocellular carcinoma cells via the wnt signaling pathway.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Sep 23. doi: 10.3892/ijo.2013.2107.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2107](#)

AUTORES / AUTHORS: - Xu MX; Zhao L; Deng C; Yang L; Wang Y; Guo T; Li L; Lin J; Zhang L

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Basic Medical College, Zhengzhou University, Zhengzhou 450001, P.R. China.

RESUMEN / SUMMARY: - Curcumin from the rhizome of *Curcuma longa* (zingiberaceae) has been reported to be a chemopreventive agent that affects cell proliferation by arresting the cell cycle in G2 and modulating the wnt signaling pathway. We found that curcumin inhibits proliferation and induces apoptosis of human hepatocellular carcinoma (HCC) cells in a concentration-dependent manner. We identified that curcumin interrupts wnt signaling by decreasing beta-catenin activity, which in turn suppresses the expression of beta-catenin target genes (c-myc, VEGF and cyclin D1). Our results from molecular simulation of curcumin binding to Dvl2 protein and from binding free energy calculations suggest that curcumin may prevent axin recruitment to cellular membrane in order to maintain the functional beta-catenin destruction complex in normal cells. This results in beta-catenin being unable to accumulate in the nucleus, depriving the protein of its ability to bind with lymphoid enhancer factor/T cell-specific transcription factor (Lef/Tcf) and repressing its activation of target gene transcription. This may be one mechanism through which curcumin inhibits proliferation and induces apoptosis of HCC cells.

[320]

TÍTULO / TITLE: - The expression of histone deacetylase 4 is associated with prednisone poor-response in childhood acute lymphoblastic leukemia.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Oct;37(10):1200-7. doi: 10.1016/j.leukres.2013.07.016. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.016](#)

AUTORES / AUTHORS: - Gruhn B; Naumann T; Gruner D; Walther M; Wittig S; Becker S; Beck JF; Sonnemann J

INSTITUCIÓN / INSTITUTION: - Jena University Hospital, Children's Clinic, Department of Pediatric Hematology and Oncology, Jena, Germany.

RESUMEN / SUMMARY: - This study aimed at the identification of histone deacetylase (HDAC) isoforms relevant for childhood acute lymphoblastic leukemia (ALL). Expression of HDAC1-11 was determined in 93 primary ALL and eight healthy donor samples. HDAC1, HDAC2 and HDAC8 showed significantly higher expressions in ALL samples. Correlation analysis of HDAC expression with clinicopathological parameters revealed that high HDAC1, HDAC2, HDAC4 and HDAC11 levels were significantly associated with unfavorable prognostic factors. Particularly, high HDAC4 expression was associated

with high initial leukocyte count, T cell ALL and prednisone poor-response. siRNA-mediated inhibition of HDAC4 sensitized a T-ALL cell line to etoposide-induced cell death. In conclusion, our data point to HDAC4 as drug target in childhood ALL, especially in prednisone poor-responders.

[321]

TÍTULO / TITLE: - E2F1-mediated DNA damage is implicated in 8-Cl-adenosine-induced chromosome missegregation and apoptosis in human lung cancer H1299 cells.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1797-1](#)

AUTORES / AUTHORS: - Han YY; Zhou Z; Cao JX; Jin YQ; Li SY; Ni JH; An GS; Zhang YX; Jia HT

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Capital Medical University, You An Men 8, Beijing, 100069, People's Republic of China.

RESUMEN / SUMMARY: - Although E2F1-mediated DNA double-stranded breaks (DSBs) and tetraploid have been extensively studied, the role of E2F1 in mitotic catastrophe is still unknown. We have previously shown that 8-chloro-adenosine (8-Cl-Ado) induces DNA DSBs and aberrant mitosis in human lung cancer cells, followed by delayed apoptosis. Here, we demonstrate that E2F1-mediated DNA damage is implicated in 8-Cl-Ado-induced chromosome missegregation and apoptosis in lung cancer H1299 cells. We showed that E2F1 was accumulated upon 8-Cl-Ado-induced DNA DSBs. Induction of E2F1 by 8-Cl-Ado caused DNA damage in cycling cells including M cells. In contrast, silencing of E2F1 expression decreased 8-Cl-Ado-induced DNA DSBs, particularly eliminated E2F1-mediated mitotic DNA damage. Over-expression of E2F1 and/or 8-Cl-Ado exposure resulted in aberrant mitotic spindles and chromosome segregation errors. Furthermore, over-expression of E2F1 expression enhanced 8-Cl-Ado-induced apoptosis. Together, our data indicate that E2F1-mediated DNA damage, in particular mitotic DNA damage, is an important fraction of 8-Cl-Ado-induced DNA damage, which is implicated in 8-Cl-Ado-induced mitotic catastrophe and delayed apoptosis. Induction of E2F1 by 8-Cl-Ado may contribute at least partly to the drug-inhibited proliferation of cancer cells.

[322]

TÍTULO / TITLE: - Gene expression profiles for the prediction of progression-free survival in diffuse large B cell lymphoma: results of a DASL assay.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Aug 24.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1884-0](#)

AUTORES / AUTHORS: - Kim SJ; Sohn I; Do IG; Jung SH; Ko YH; Yoo HY; Paik S; Kim WS

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, 135-710, South Korea.

RESUMEN / SUMMARY: - We performed the whole genome cDNA-mediated annealing, selection and ligation assay with 164 formalin-fixed paraffin-embedded (FFPE) tumor samples to develop robust prognostic gene expression profiles in patients with diffuse large B cell lymphoma. The prognostic gene expression profiles were developed and validated by a gradient lasso and leave-one-out cross-validation process. We identified a set of genes whose expression provided prognostic indicators from whole data set (PRKCDBP, CASP10, FAM3C, KCNK12, MAN1A2, PRND, RAB1A, TMEM39B, SLC6A6, MMP12, FEM1B, C3orf37, RBP1, HK1, LOC400464, KIAA0746, and SLC25A23). This gene expression profile-based risk model could classify patients into two cross-validated risk groups with a significant difference in 5-year progression-free survival rates (71.1 vs. 45.5 %) and with a hazard ratio for recurrence of 2.45 (95 % CI, 1.44-4.16, P = 0.001). This model provided prognostic information independent of the International Prognostic Index (IPI), and discriminated high-risk group from patients belong to high/high-intermediate risk of IPI and activated B cell-like type. Thus, gene expression profiling from FFPE could provide additional prognostic information for diffuse large B cell lymphoma and our data underscore the need for development of risk-adapted treatment strategies based on gene expression profiles.

[323]

TÍTULO / TITLE: - Radiological assessment of response to neoadjuvant transcatheter hepatic therapy with irinotecan-eluting beads (DEBIRI[®]) for colorectal liver metastases does not predict tumour destruction or long-term outcome.

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

REVISTA / JOURNAL: - Eur J Surg Oncol. 2013 Oct;39(10):1122-8. doi: 10.1016/j.ejso.2013.07.087. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.07.087](https://doi.org/10.1016/j.ejso.2013.07.087)

AUTORES / AUTHORS: - Jones RP; Stattner S; Dunne DF; O'Grady E; Smethurst A; Terlizzo M; Malik HZ; Fenwick SW; Poston GJ

INSTITUCIÓN / INSTITUTION: - School of Cancer Studies, Institute of Translational Medicine, University of Liverpool, Liverpool, UK; Northwestern Hepatobiliary Unit, Aintree University Hospital, Liverpool, UK. Electronic address: robjones@liv.ac.uk.

RESUMEN / SUMMARY: - INTRODUCTION: Transcatheter hepatic therapy with irinotecan-eluting beads (DEBIRI[®]) allows targeted delivery of irinotecan direct to liver tissue and colorectal liver metastases (CRLM). Accurate assessment of tumour response to therapy is vital to guide optimal treatment. Preliminary work has suggested existing criteria for radiological response may not reflect pathological response after

neoadjuvant DEBIRI. This study assessed the relationship between existing and novel radiological response criteria and pathological tumour response as well as long-term outcome. METHODS: Patients with easily resectable CRLM were treated with DEBIRI 4 weeks prior to resection and pathological tumour response graded using a validated system. Radiological response was assessed using RECIST and novel morphological response criteria. RESULTS: Twenty-two patients with 37 lesions were treated with DEBIRI. Median residual tumour was 20% (range 0-80), median necrosis 45% (10-100) and median fibrosis 10% (10-70). Twenty patients (91%) demonstrated stable disease by RECIST, with 11 (50%) demonstrating partial morphological response. Neither radiological response criteria correlated with pathological response. Overall median disease free survival (DFS) was 13.6 months (95% CI 4.7-22.5). Radiological response was not associated with DFS. CONCLUSION: Existing criteria reporting short-term radiological response to DEBIRI do not accurately predict pathological tumour response or long-term outcome. Further work is necessary to define the optimum timing and method of assessing response to DEBIRI.

[324]

TÍTULO / TITLE: - Loss of CDX2/CK20 Expression Is Associated With Poorly Differentiated Carcinoma, the CpG Island Methylator Phenotype, and Adverse Prognosis in Microsatellite-unstable Colorectal Cancer.

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

REVISTA / JOURNAL: - Am J Surg Pathol. 2013 Oct;37(10):1532-41. doi: 10.1097/PAS.0b013e31829ab1c1.

●● Enlace al texto completo (gratis o de pago) [1097/PAS.0b013e31829ab1c1](#)

AUTORES / AUTHORS: - Kim JH; Rhee YY; Bae JM; Cho NY; Kang GH

INSTITUCIÓN / INSTITUTION: - *Department of Pathology double daggerLaboratory of Epigenetics, Cancer Research Institute, Seoul National University College of Medicine daggerDepartment of Pathology, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - Several previous studies have demonstrated that the CDX2-negative (CDX2) and/or CK20-negative (CK20) phenotypes of colorectal cancers (CRCs) might be associated with high levels of microsatellite instability (MSI-H). The aim of this study was to investigate the clinicopathologic and molecular features of MSI-H CRCs with different CDX2/CK20 expression statuses. The CDX2 and CK20 expression statuses were immunohistochemically evaluated in 109 MSI-H CRC tissue samples, and the correlations of these statuses with clinicopathologic, molecular, and survival data were statistically analyzed. Of the 109 MSI-H CRCs, 15 were CDX2 (13.8%), and 19 were CK20 (17.4%). The simultaneous loss of CDX2 and CK20 expression (CDX2/CK20) was observed in 9 cases (8.3%). CDX2 loss was correlated with lymph node metastasis, poor differentiation, MLH1 loss, the mutation of BRAF, and CpG island methylator

phenotype-high (CIMP-H) status. Right-sided tumor location, nodal metastasis, poor differentiation, and CIMP-H status were significant characteristics of CK20 tumors. The CDX2/CK20 phenotype was associated with older age (above 56 y), higher stage (stage III or IV), deep invasion (pT3 or pT4), lymph node metastasis (pN1 or pN2), poor differentiation (nonmedullary/non-signet ring cell type), the mutation of BRAF, and CIMP-H status among MSI-H CRCs. Patients with CDX2/CK20 tumors exhibited worse overall and disease-free survival compared with the patients with CDX2 and/or CK20 tumors ($P < 0.001$). In the multivariate analysis for disease-free survival, the CDX2/CK20 phenotype was an independent prognostic factor for MSI-H CRC ($P = 0.030$, hazard ratio = 3.288). The CDX2/CK20 phenotype defines a distinct subgroup of MSI-H CRCs with poor differentiation, CIMP-H status, and unfavorable prognosis.

[325]

TÍTULO / TITLE: - Long-term prognosis of childhood acute promyelocytic leukaemia with arsenic trioxide administration in induction and consolidation chemotherapy phases: a single-centre experience.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Aug 23. doi: 10.1111/ejh.12194.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12194](#)

AUTORES / AUTHORS: - Cheng Y; Zhang L; Wu J; Lu A; Wang B; Liu G

INSTITUCIÓN / INSTITUTION: - Department of Paediatrics, Medical School, Peking University, The Affiliated People's Hospital of Peking University, Beijing, China.

RESUMEN / SUMMARY: - **OBJECTIVES:** The efficacy of all-trans retinoic acid (ATRA) and arsenic trioxide (As₂O₃) as induction therapy for adult acute promyelocytic leukaemia (APL) has been documented in several clinical trials. However, the role of ATRA/As₂O₃ combination in induction and consolidation therapy in children remains unclear. Here, we report the efficacy of combined treatment with As₂O₃ and ATRA as induction and consolidation chemotherapy to treat newly diagnosed childhood APL. **METHODS:** From 1998 to 2011, 43 children with newly diagnosed APL received induction and consolidation chemotherapy with ATRA and As₂O₃ (Protocol B). Rates of complete remission (CR), event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) and drug toxicity were compared between children treated with Protocol B and 25 others treated previously with ATRA alone as induction chemotherapy (Protocol A). **RESULTS:** Of 43 patients treated with Protocol B, 41 (95.4%) achieved CR (two died of intracranial haemorrhage on day 10 and 14). In contrast, only 20 (80%) of 25 patients treated with Protocol A achieved CR. Thus, the CR rate was significantly lower in patients receiving induction chemotherapy with Protocol A than in those treated with Protocol B ($P = 0.045$, $\chi^2 = 6.508$). Of the 41 patients who achieved CR on induction therapy with Protocol B, 40 also received consolidation therapy. Molecular relapse, but no overt morphological relapse,

occurred in one patient at 25 months after diagnosis; this patient regained CR status with As2 O3 treatment. With a median follow-up period of 75 months, estimated EFS, DFS and OS rates were 92.5 +/- 4.2%, 97.1 +/- 2.9% and 95.3 +/- 3.2%, respectively, for Protocol B. In contrast, with a median follow-up of 127 months, the EFS, DFS and OS rates at 75 months were 70.4 +/- 9.4%, 76.4 +/- 9.2% and 70.4 +/- 9.4%, respectively, for Protocol A. Thus, patients treated with Protocol A showed significantly lower EFS (P = 0.021) and OS (P = 0.007) rates than those treated with Protocol B. CONCLUSIONS: Application of As2 O3 and ATRA as induction and consolidation chemotherapy resulted in excellent outcomes and improved long-term prognosis in children with newly diagnosed APL.

[326]

TÍTULO / TITLE: - Inhibition of the tumour necrosis factor-alpha autocrine loop enhances the sensitivity of multiple myeloma cells to anticancer drugs.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 7. pii: S0959-8049(13)00560-1. doi: 10.1016/j.ejca.2013.07.010.

●● Enlace al texto completo (gratuito o de pago) [1016/j.ejca.2013.07.010](#)

AUTORES / AUTHORS: - Tsubaki M; Komai M; Itoh T; Imano M; Sakamoto K; Shimaoka H; Ogawa N; Mashimo K; Fujiwara D; Takeda T; Mukai J; Sakaguchi K; Satou T; Nishida S

INSTITUCIÓN / INSTITUTION: - Division of Pharmacotherapy, Kinki University School of Pharmacy, Kowakae, Higashi-Osaka, Japan.

RESUMEN / SUMMARY: - Several autocrine soluble factors, including macrophage inflammatory protein-1alpha and tumour necrosis factor-alpha (TNF-alpha), promote the survival and growth of multiple myeloma (MM) cells. We hypothesised that inhibition of the TNF-alpha autocrine loop may enhance the cytotoxic effect of anticancer drugs in MM cell lines. In the present study, a TNF-alpha-neutralizing antibody suppressed cell proliferation and enhanced the cytotoxic effect of anticancer drugs on MM cells. In addition, combination treatment with the TNF-alpha-neutralizing antibody and the chemotherapy agent melphalan inhibited nuclear factor kappaB (NF-kappaB) p65 nuclear translocation and mammalian target of rapamycin (mTOR) activation and upregulated the expression of Bax and Bim. Treatment of ARH-77 cells with the NF-kappaB inhibitor dimethyl fumarate or the mTOR inhibitor rapamycin suppressed NF-kappaB p65 nuclear translocation and enhanced the cytotoxic effect of melphalan. Furthermore, infliximab, a monoclonal antibody against TNF-alpha, also enhanced the cytotoxic effect of anticancer drugs in ARH-77 cells. These results indicated that TNF-alpha-neutralizing antibodies or infliximab enhanced the cytotoxic effect of anticancer drugs by suppressing the TNF receptor/mTOR/NF-kappaB pathways. The inhibition of TNF-alpha may thus provide a new therapeutic approach to control tumour progression and bone destruction in MM patients.

[327]

TÍTULO / TITLE: - Expression of deleted in liver cancer 1 and plasminogen activator inhibitor 1 protein in ovarian carcinoma and their clinical significance.

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

REVISTA / JOURNAL: - J Exp Clin Cancer Res. 2013 Aug 30;32(1):60.

●● Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-60](#)

AUTORES / AUTHORS: - Ren F; Shi H; Zhang G; Zhang R

RESUMEN / SUMMARY: - BACKGROUND: The deleted in liver cancer 1 (DLC1) and plasminogen activator inhibitor 1 (PAI-1) are known to be closely associated with tumor growth and metastasis in several kinds of human tumors. The aim of this study was to investigate the expression of DLC1 and PAI-1 in ovarian carcinoma, and evaluate their relations with the prognosis of ovarian carcinoma. METHODS: Immunohistochemical staining and Western blot were used to examine the expressions of DLC1 and PAI-1 protein in 25 specimens normal ovarian tissues, 52 specimens of serous cystadenocarcinoma tissues and 23 specimens of mucinous cystadenocarcinoma tissues. Chi-square test, Logistic regression and Partial Correlate analysis were performed to evaluate the association between DLC1 and PAI-1 with clinicopathological characteristics. Overall survival was estimated by Kaplan-Meier curves and multivariate Cox analysis. The relationships between DLC1 and PAI-1 protein expression were analyzed by Pearson's correlation coefficient. RESULTS: The expression of DLC1 protein in ovarian carcinoma tissues was significantly lower than that in normal ovarian tissues, but it was converse for PAI-1. In ovarian carcinoma, the expression of DLC1 was significantly associated with advanced FIGO stage, ascites and positive lymph node metastasis, whereas PAI-1 protein was closely related with advanced FIGO stage, poor histological differentiation and lymph node metastasis. The expression of DLC1 was negatively correlated with PAI-1 in ovarian carcinoma. Ovarian cancer patients with negative expression of DLC1 and positive expression of PAI-1 had the worst overall survival time compared to other patients. CONCLUSIONS: The expression of DLC1 and PAI-1 were closely related with the metastasis and invasion of ovarian carcinoma, only the combination of DLC1 and PAI-1 could serve as an independent prognostic factor of ovarian carcinoma.

[328]

TÍTULO / TITLE: - Defective expression of Protein 4.1N is correlated to tumor progression, aggressive behaviors and chemotherapy resistance in epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Aug 27. pii: S0090-8258(13)01100-1. doi: 10.1016/j.ygyno.2013.08.015.

●● Enlace al texto completo (gratis o de pago) [1016/j.ygyno.2013.08.015](https://doi.org/10.1016/j.ygyno.2013.08.015)

AUTORES / AUTHORS: - Xi C; Ren C; Hu A; Lin J; Yao Q; Wang Y; Gao Z; An X; Liu C

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Peking University Health Science Center, Beijing 100191, China.

RESUMEN / SUMMARY: - OBJECTIVE: Protein 4.1N (4.1N) is a member of the Protein 4.1 family that is involved in cellular processes such as cell adhesion, migration and signaling. In this study, we evaluated the expression of 4.1N protein and its potential roles in epithelial ovarian cancer (EOC) tumorigenesis and progression. METHODS: 4.1N protein expression was investigated in a total of 280 samples including 74 normal tissues, 35 benign, 30 borderline and 141 malignant epithelial ovarian tumors by immunohistochemistry. Correlation between 4.1N expression levels and clinicopathologic features was statistically analyzed. The expression of 4.1N in EOC cell lines was examined by western blotting. RESULTS: Immunohistochemistry analysis revealed that, although there was no loss of 4.1N expression in normal tissues and benign tumors, absence of Protein 4.1N was significantly more common in EOCs (44.0%) than in borderline tumors (3.3%) ($p < 0.001$). Furthermore, loss or decreased expression of 4.1N protein expression was correlated with malignant potential of the tumors (14.3% in benign tumors, 56.7% in borderline tumors and 92.9% in malignancy) ($p < 0.001$). In EOC samples, loss of 4.1N protein was significantly associated with advanced-stage ($p = 0.004$), ascites ($p = 0.009$), omental metastasis ($p = 0.018$), suboptimal debulking ($p = 0.024$), poorly histological differentiation ($p = 0.009$), high-grade serous carcinoma ($p = 0.001$), short progression-free-survival ($p = 0.018$) and poor chemosensitivity to first-line chemotherapy ($p = 0.029$). Moreover, western blotting analysis revealed that expression of 4.1N protein was lost in 4/8 (50%) EOC cell lines. CONCLUSIONS: 4.1N protein expression level was significantly decreased during malignant transformation of epithelial ovarian tumors and that loss of 4.1N expression was closely correlated to poorly differentiated and biologically aggressive EOCs.

[329]

TÍTULO / TITLE: - Does BRAF V600E Mutation Predict Aggressive Features in Papillary Thyroid Cancer? Results From Four Endocrine Surgery Centers.

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

REVISTA / JOURNAL: - J Clin Endocrinol Metab. 2013 Sep;98(9):3702-12. doi: 10.1210/jc.2013-1584. Epub 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1210/jc.2013-1584](https://doi.org/10.1210/jc.2013-1584)

AUTORES / AUTHORS: - Li C; Aragon Han P; Lee KC; Lee LC; Fox AC; Beninato T; Thiess M; Dy BM; Sebo TJ; Thompson GB; Grant CS; Giordano TJ; Gauger PG; Doherty GM; Fahey TJ 3rd; Bishop J; Eshleman JR; Umbricht CB; Schneider EB; Zeiger MA

INSTITUCIÓN / INSTITUTION: - MD,Oncology, and Cellular and Molecular Medicine, Chief of Endocrine Surgery, Johns Hopkins Hospital, 600 North Wolfe Street, Department of Surgery, Blalock 606, Baltimore, Maryland 21287. mzeiger@jhmi.edu.

RESUMEN / SUMMARY: - Background: Existing evidence is controversial regarding the association between BRAF mutation status and aggressive features of papillary thyroid cancer (PTC). Specifically, no study has incorporated multiple surgical practices performing routine central lymph node dissection (CLND) and thus has patients who are truly evaluable for the presence or absence of central lymph node metastases (CLNMs). Methods: Consecutive patients who underwent total thyroidectomy and routine CLND at 4 tertiary endocrine surgery centers were retrospectively reviewed. Descriptive and bivariable analyses examined demographic, patient, and tumor-related factors. Multivariable analyses examined the odds of CLNM associated with positive BRAF status. Results: In patients with classical variant PTC, bivariate analysis found no significant associations between BRAF mutation and aggressive clinicopathologic features; multivariate analysis demonstrated that BRAF status was not an independent predictor of CLNM. When all patients with PTC were analyzed, including those with aggressive or follicular subtypes, bivariate analysis showed BRAF mutation to be associated with LNM, advanced American Joint Committee on Cancer (AJCC) stage, and histologic subtype. Multivariable analyses showed BRAF, age, size, and extrathyroidal extension to be associated with CLNM. Conclusion: Although BRAF mutation was found to be an independent predictor of central LNM in the overall cohort of patients with PTC, this relationship lost significance when only classical variant PTC was included in the analysis. The usefulness of BRAF in predicting the presence of LNM remains questionable. Prospective studies are needed before BRAF mutation can be considered a reliable factor to guide the treatment of patients with PTC, specifically whether to perform prophylactic CLND.

[330]

TÍTULO / TITLE: - Progesterone protects ovarian cancer cells from cisplatin-induced inhibitory effects through progesterone receptor membrane component 1/2 as well as AKT signaling.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2488-94. doi: 10.3892/or.2013.2680. Epub 2013 Aug 21.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2680](#)

AUTORES / AUTHORS: - Zhu X; Han Y; Fang Z; Wu W; Ji M; Teng F; Zhu W; Yang X; Jia X; Zhang C

INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine, Jiangsu Provincial Hospital of Traditional Chinese Medicine, Nanjing, Jiangsu 210029, P.R. China.

RESUMEN / SUMMARY: - Progesterone, also known as P4 (pregn-4-ene-3, 20-dione), is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Despite the physiological effects, P4 is also effective for the treatment of numerous pathological states, such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus as well as cancer. Considering the hormone microenvironment of gynecological cancers, P4 should be particularly noted in ovarian cancer. The present study demonstrated that P4 protected the ovarian cancer cell line HO-8910 from cisplatin (CDDP)-induced cell cycle arrest and restored the cell migratory capability following treatment of CDDP. Mechanistically, both progesterone receptor membrane component 1 (PGRMC1) and the progesterone receptor (PGR) were decreased in the cells treated with CDDP plus P4, while the level of progesterone receptor membrane component 2 (PGRMC2) was significantly elevated. Reversely, in the HO-8910 cells treated with CDDP alone, levels of both PGRMC1 and PGR were increased while the level of PGRMC2 was decreased. In addition to the receptor expression profile, the PI3K/AKT signaling pathway was also involved in the action of P4 in the CDDP-resistant HO-8910 cells, and a chemical inhibitor for PI3K, LY294002, significantly abolished the anti-apoptotic effect of P4. Consequently, the addition of a PI3K inhibitor to CDDP-based chemotherapy may have a more beneficial application for ovarian cancer therapy.

[331]

TÍTULO / TITLE: - Impact of body mass index on estradiol depletion by aromatase inhibitors in postmenopausal women with early breast cancer.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 17;109(6):1522-7. doi: 10.1038/bjc.2013.499. Epub 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.499](#)

AUTORES / AUTHORS: - Pfeiler G; Konigsberg R; Hadji P; Fitzal F; Maroske M; Dressel-Ban G; Zellinger J; Exner R; Seifert M; Singer C; Gnant M; Dubsy P

INSTITUCIÓN / INSTITUTION: - Division of Gynecology and Gynecological Oncology, Department of OB/GYN, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - Background:Body mass index (BMI) has an impact on survival outcome in patients treated with aromatase inhibitors (AIs). Obesity is associated with an increased body aromatisation and may be a cause of insufficient estradiol depletion.Methods:Sixty-eight postmenopausal oestrogen receptor-positive patients with early breast cancer were prospectively included in this study. Follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol were analysed immediately in the clinical routine lab and in a dedicated central lab before (T1) and 3 months after start with aromatase inhibitors (T2).Results:A total of 40 patients were normal or

overweight (non-obese: BMI 18.5-29.9 kg m⁻²) and 28 were obese (BMI ≥ 30 kg m⁻²). Aromatase inhibitors significantly suppressed estradiol serum levels (T1: 19.5 pg ml⁻¹, T2: 10.5 pg ml⁻¹, P<0.01) and increased FSH serum levels (T1: 70.2 mIU ml⁻¹, T2: 75.7 mIU ml⁻¹, P<0.05). However, after 3 months of AI treatment, estradiol levels of obese patients were nonsignificantly higher compared with non-obese patients (12.5 pg ml⁻¹ vs 9.0 pg ml⁻¹, P=0.1). This difference was reflected by significantly lower FSH serum levels in obese compared with non-obese patients (65.5 mIU ml⁻¹ vs 84.6 mIU ml⁻¹, P<0.01). The significant effects of BMI on FSH serum levels could be detected both in the routine as well as in the dedicated central lab. Conclusion: Aromatase inhibitors are less efficient at suppressing estradiol serum levels in obese when compared with non-obese women.

[332]

TÍTULO / TITLE: - Curcumin-loaded nanoparticles induce apoptotic cell death through regulation of the function of MDR1 and reactive oxygen species in cisplatin-resistant CAR human oral cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1141-50. doi: 10.3892/ijo.2013.2050. Epub 2013 Aug 5.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2050](#)

AUTORES / AUTHORS: - Chang PY; Peng SF; Lee CY; Lu CC; Tsai SC; Shieh TM; Wu TS; Tu MG; Chen MY; Yang JS

INSTITUCIÓN / INSTITUTION: - Department of Dentistry, China Medical University, Taichung 404, Taiwan, R.O.C.

RESUMEN / SUMMARY: - Curcumin is a polyphenolic compound which possesses anticancer potential. It has been shown to induce cell death in a variety of cancer cells, however, its effect on CAL27 cisplatin-resistant human oral cancer cells (CAR cells) has not been elucidated to date. The low water solubility of curcumin which leads to poor bioavailability, however, has been highlighted as a major limiting factor. In this study, we utilized water-soluble PLGA curcumin nanoparticles (Cur-NPs), and investigated the effects of Cur-NPs on CAR cells. The results showed Cur-NPs induced apoptosis in CAR cells but exhibited low cytotoxicity to normal human gingival fibroblasts (HGFs) and normal human oral keratinocytes (OKs). Cur-NPs triggered DNA concentration, fragmentation and subsequent apoptosis. Compared to untreated CAR cells, a more detectable amount of Calcein-AM accumulation was found inside the treated CAR cells. Cur-NPs suppressed the protein and mRNA expression levels of MDR1. Both the activity and the expression levels of caspase-3 and caspase-9 were elevated in the treated CAR cells. The Cur-NP-triggered apoptosis was blocked by specific inhibitors of pan-caspase (z-VAD-fmk), caspase-3 (z-DEVD-fmk), caspase-9 (z-LEHD-fmk) and antioxidant agent (N-acetylcysteine; NAC). Cur-NPs increased reactive

oxygen species (ROS) production, upregulated the protein expression levels of cleaved caspase-3/caspase-9, cytochrome c, Apaf-1, AIF, Bax and downregulated the protein levels of Bcl-2. Our results suggest that Cur-NPs triggered the intrinsic apoptotic pathway through regulating the function of multiple drug resistance protein 1 (MDR1) and the production of reactive oxygen species (ROS) in CAR cells. Cur-NPs could be potentially efficacious in the treatment of cisplatin-resistant human oral cancer.

[333]

TÍTULO / TITLE: - Targeting cyclin-dependent kinases in anti-neoplastic therapy.

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

REVISTA / JOURNAL: - Curr Opin Cell Biol. 2013 Sep 6. pii: S0955-0674(13)00146-4. doi: 10.1016/j.ceb.2013.08.004.

●● Enlace al texto completo (gratis o de pago) 1016/j.ceb.2013.08.004

AUTORES / AUTHORS: - Bruyere C; Meijer L

INSTITUCIÓN / INSTITUTION: - ManRos Therapeutics, Centre de Perharidy, 29680 Roscoff, France.

RESUMEN / SUMMARY: - Cell cycle progression is controlled by sequential activation of cyclin-dependent kinases (CDKs), which are often deregulated in cancer. Consequently numerous pharmacological inhibitors of CDKs have been developed with the aim of treating cancers. The article briefly reviews CDK inhibitors and their use to treat cancers, with specific focus on the use of biomarkers and drugs combination to improve their therapeutic efficacy.

[334]

TÍTULO / TITLE: - Development of antiangiogenic therapies for ovarian cancer.

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

REVISTA / JOURNAL: - Eur J Gynaecol Oncol. 2013;34(4):303-6.

AUTORES / AUTHORS: - Markowska A; Lubin J; Madry R; Markowska J

INSTITUCIÓN / INSTITUTION: - Department of Perinatology and Gynecology, Karol Marcinkowski University of Medical Science, Poznan.

RESUMEN / SUMMARY: - Angiogenesis is a dynamic process which leads to a development of cancer and metastases. The most recognized and dominant prognostic factor is vascular endothelial growth factor (VEGF) and its receptors. VEGF was identified in 1989. There are three receptors for VEGF: VEGFR1 (VEGF receptor 1) and VEGFR2 that play the role in angiogenesis and development of ascites, and VEGFR3 is critical for lymphangiogenesis. There is bevacizumab—a new drug, monoclonal antibody that can block connection VEGF to its receptors. The first notification of activity of bevacizumab in ovarian cancer was in 2005. The aim of the article is to show some clinical trials in ovarian cancer and their results. The bevacizumab was registered

in November 2011 in first line with standard chemotherapy in ovarian cancer. There is a new weapon against this disease.

[335]

TÍTULO / TITLE: - Wogonin induces apoptosis by suppressing E6 and E7 expressions and activating intrinsic signaling pathways in HPV-16 cervical cancer cells.

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

REVISTA / JOURNAL: - Cell Biol Toxicol. 2013 Aug;29(4):259-72. doi: 10.1007/s10565-013-9251-4. Epub 2013 Aug 18.

●● Enlace al texto completo (gratis o de pago) [1007/s10565-013-9251-4](#)

AUTORES / AUTHORS: - Kim MS; Bak Y; Park YS; Lee DH; Kim JH; Kang JW; Song HH; Oh SR; Yoon do Y

INSTITUCIÓN / INSTITUTION: - Department of Bioscience and Biotechnology, Bio/Molecular Informatics Center, Konkuk University, 1 Hwayang-dong, Gwangjin-gu, Seoul, 143-701, Republic of Korea.

RESUMEN / SUMMARY: - Wogonin is a flavonoid compound extracted from *Scutellaria baicalensis* and is well known as a benzodiazepine receptor ligand with anxiolytic effects. Many recent studies have demonstrated that wogonin modulates angiogenesis, proliferation, invasion, and tumor progress in various cancer tissues. We further explored the mechanism of action of wogonin on cervical cancer cells that contain or lack human papillomavirus (HPV) DNA. Wogonin was cytotoxic to HPV 16 (+) cervical cancer cells, SiHa and CaSki, but not to HPV-negative cells. We demonstrated that wogonin induced apoptosis by suppressing the expressions of the E6 and E7 viral oncogenes in HPV-infected cervical cancer CaSki and SiHa cells. The modulation of p53 and protein retinoblastoma (pRb) were also triggered by the suppression of E6 and E7 expressions. However, p53 was not altered in HPV-negative cervical cancer C33A cells. Moreover, wogonin modulated the mitochondrial membrane potential and the expression of pro- and anti-apoptotic factors such as Bax and Bcl-2. Wogonin also provoked the cleavage of caspase-3, caspase-9, and poly ADP ribose polymerase. After transfection of siRNAs to target E6 and E7, additional restoration of p53 and pRb was not induced, but processing of caspases and PARP was increased compared with wogonin treatment alone. Together, our findings demonstrated that wogonin effectively promotes apoptosis by downregulating E6 and E7 expressions and promoting intrinsic apoptosis in human cervical cancer cells.

[336]

TÍTULO / TITLE: - Anticancer effect of genistein on BG-1 ovarian cancer growth induced by 17 beta-estradiol or bisphenol A via the suppression of the crosstalk between estrogen receptor alpha and insulin-like growth factor-1 receptor signaling pathways.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Aug 8;272(3):637-646. doi: 10.1016/j.taap.2013.07.027.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.07.027](#)

AUTORES / AUTHORS: - Hwang KA; Park MA; Kang NH; Yi BR; Hyun SH; Jeung EB; Choi KC

INSTITUCIÓN / INSTITUTION: - Laboratory of Veterinary Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea.

RESUMEN / SUMMARY: - The interaction between estrogen receptor (ER) and insulin-like growth factor-1 receptor (IGF-1R) signaling pathway plays an important role in proliferation of and resistance to endocrine therapy to estrogen dependent cancers. Estrogen (E2) upregulates the expression of components of IGF-1 system and induces the downstream of mitogenic signaling cascades via phosphorylation of insulin receptor substrate-1 (IRS-1). In the present study, we evaluated the xenoestrogenic effect of bisphenol A (BPA) and antiproliferative activity of genistein (GEN) in accordance with the influence on this crosstalk. BPA was determined to affect this crosstalk by upregulating mRNA expressions of ERalpha and IGF-1R and inducing phosphorylation of IRS-1 and Akt in protein level in BG-1 ovarian cancer cells as E2 did. In the mouse model xenografted with BG-1 cells, BPA significantly increased a tumor burden of mice and expressions of ERalpha, pIRS-1, and cyclin D1 in tumor mass compared to vehicle, indicating that BPA induces ovarian cancer growth by promoting the crosstalk between ER and IGF-1R signals. On the other hand, GEN effectively reversed estrogenicity of BPA by reversing mRNA and protein expressions of ERalpha, IGF-1R, pIRS-1, and pAkt induced by BPA in cellular model and also significantly decreased tumor growth and in vivo expressions of ERalpha, pIRS-1, and pAkt in xenografted mouse model. Also, GEN was confirmed to have an antiproliferative effect by inducing apoptotic signaling cascades. Taken together, these results suggest that GEN effectively reversed the increased proliferation of BG-1 ovarian cancer by suppressing the crosstalk between ERalpha and IGF-1R signaling pathways upregulated by BPA or E2.

[337]

TÍTULO / TITLE: - Systems Biology Analysis of Kinase Inhibitor Action in Leukemia Treatments.

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

REVISTA / JOURNAL: - Biomed Tech (Berl). 2013 Sep 7. pii: /j/bmte.2013.58.issue-s1-M/bmt-2013-4306/bmt-2013-4306.xml. doi: 10.1515/bmt-2013-4306.

●● Enlace al texto completo (gratis o de pago) [1515/bmt-2013-4306](#)

AUTORES / AUTHORS: - Colinge J

[338]

TÍTULO / TITLE: - Phenethyl isothiocyanate induces apoptosis of cholangiocarcinoma cells through interruption of glutathione and mitochondrial pathway.

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

REVISTA / JOURNAL: - Naunyn Schmiedebergs Arch Pharmacol. 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1007/s00210-013-0906-8](#)

AUTORES / AUTHORS: - Tuskorn O; Prawan A; Senggunprai L; Kukongviriyapan U; Kukongviriyapan V

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, 40002.

RESUMEN / SUMMARY: - Phenethyl isothiocyanate (PEITC) is a natural isothiocyanate with anticancer activity against many drug-resistant cancer cells. A body of evidence suggests that PEITC enhances oxidative stress leading to cancer cell death. Cholangiocarcinoma (CCA) is an aggressive bile duct cancer with resistance to chemotherapeutic drugs. PEITC rapidly kills KKU-100 CCA cells with concurrent induction of cellular glutathione depletion, superoxide formation, and loss of mitochondrial transmembrane potential. The loss was associated with increased Bax and decreased Bcl-xl proteins followed by the release of cytochrome c and the activation of caspase-9 and -3. Although TEMPOL could prevent superoxide formation, it did not prevent the disruption of glutathione (GSH) redox, mitochondrial dysfunction, and cell death. On the other hand, N-acetylcysteine could prevent the events and cell death. It was concluded that disruption of GSH redox but not superoxide formation may be an initial step leading to mitochondrial injury. PEITC could be a promising chemopreventive agent for CCA.

[339]

TÍTULO / TITLE: - Erratum to: Phenethyl isothiocyanate induces apoptosis of cholangiocarcinoma cells through interruption of glutathione and mitochondrial pathway.

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

REVISTA / JOURNAL: - Naunyn Schmiedebergs Arch Pharmacol. 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1007/s00210-013-0914-8](#)

AUTORES / AUTHORS: - Tuskorn O; Prawan A; Senggunprai L; Kukongviriyapan U; Kukongviriyapan V

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, 40002.

[340]

TÍTULO / TITLE: - Efficacy of Chemotherapy in BRCA1/2 Mutation Carrier Ovarian Cancer in the Setting of PARP Inhibitor Resistance: A Multi-Institutional Study.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5485-5493. Epub 2013 Aug 6.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-1262](#)

AUTORES / AUTHORS: - Ang JE; Gourley C; Powell CB; High H; Shapira-Frommer R; Castonguay V; De Greve J; Atkinson T; Yap TA; Sandhu S; Banerjee S; Chen LM; Friedlander ML; Kaufman B; Oza AM; Matulonis U; Barber LJ; Kozarewa I; Fenwick K; Assiotis I; Campbell J; Chen L; de Bono JS; Gore ME; Lord CJ; Ashworth A; Kaye SB

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton; Edinburgh Cancer Research UK Center, Medical Research Council Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh; The Cancer Research UK Gene Function Laboratory; Breakthrough Breast Cancer Research Center; Tumour Profiling Unit, The Institute of Cancer Research, London, United Kingdom; University of California San Francisco, San Francisco, California; Department of Medical Oncology, Prince of Wales Clinical School, Prince of Wales Hospital, Sydney, Australia; The Chaim Sheba Medical Center, Tel Hashomer, Israel; Princess Margaret Hospital, Toronto, Canada; Oncologisch Centrum Vrije Universiteit Brussel, Brussels, Belgium; and Dana Farber Cancer Center, Boston, Massachusetts.

RESUMEN / SUMMARY: - **PURPOSE:** Preclinical data suggest that exposure to PARP inhibitors (PARPi) may compromise benefit to subsequent chemotherapy, particularly platinum-based regimens, in patients with BRCA1/2 mutation carrier ovarian cancer (PBMCO), possibly through the acquisition of secondary BRCA1/2 mutations. The efficacy of chemotherapy in the PARPi-resistant setting was therefore investigated. **EXPERIMENTAL DESIGN:** We conducted a retrospective review of PBMCO who received chemotherapy following disease progression on olaparib, administered at ≥ 200 mg twice daily for one month or more. Tumor samples were obtained in the post-olaparib setting where feasible and analyzed by massively parallel sequencing. **RESULTS:** Data were collected from 89 patients who received a median of 3 (range 1-11) lines of pre-olaparib chemotherapy. The overall objective response rate (ORR) to post-olaparib chemotherapy was 36% (24 of 67 patients) by Response Evaluation Criteria in Solid Tumors (RECIST) and 45% (35 of 78) by RECIST and/or Gynecologic Cancer InterGroup (GCI) CA125 criteria with median progression-free survival (PFS) and overall survival (OS) of 17 weeks [95% confidence interval (CI), 13-21] and 34 weeks (95% CI, 26-42), respectively. For patients receiving platinum-based chemotherapy, ORRs were 40% (19 of 48) and 49% (26/53), respectively, with a median PFS of 22 weeks (95% CI, 15-29) and OS of 45 weeks (95% CI, 15-75). An increased platinum-to-platinum interval was associated with an increased OS and likelihood of response following post-olaparib platinum. No evidence of secondary BRCA1/2 mutation was detected in tumor samples of six PARPi-resistant patients

[estimated frequency of such mutations adjusted for sample size: 0.125 (95%-CI: 0-0.375)]. CONCLUSIONS: Heavily pretreated PBMCOG who are PARPi-resistant retain the potential to respond to subsequent chemotherapy, including platinum-based agents. These data support the further development of PARPi in PBMCOG. Clin Cancer Res; 19(19); 5485-93. ©2013 AACR.

[341]

TÍTULO / TITLE: - Association of CXCL12 and CXCR4 gene polymorphisms with the susceptibility and prognosis of renal cell carcinoma.

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

REVISTA / JOURNAL: - Tissue Antigens. 2013 Sep;82(3):165-70. doi: 10.1111/tan.12170.

●● Enlace al texto completo (gratis o de pago) [1111/tan.12170](#)

AUTORES / AUTHORS: - Cai C; Wang LH; Dong Q; Wu ZJ; Li MY; Sun YH

INSTITUCIÓN / INSTITUTION: - Department of Special Clinic, Changhai Hospital, Second Military Medical University, Shanghai, 200433, China.

RESUMEN / SUMMARY: - CXCL12 and its unique receptor CXCR4, play important roles in inflammation and cancer metastasis. This study was undertaken to investigate the association of CXCL12 and CXCR4 polymorphisms with risk and prognosis of renal cell carcinoma (RCC) in the Chinese population. Blood was collected from 322 RCC patients and 402 healthy controls. The CXCL12 rs1801157G/A polymorphism and CXCR4 rs2228014C/T polymorphism were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Results showed that prevalence of CXCL12 rs1801157AA genotype was significantly increased in RCC cases than in controls [odds ratio (OR) = 3.07, 95% confidence interval (CI), 1.98-5.46, $P = 6.1 \times 10^{-6}$]; data were adjusted for age and sex]. Similarly, subjects carrying CXCR4 rs2228014CT or TT genotypes showed significantly high risk of RCC (OR = 1.77, 95% CI, 1.28-2.71, $P = 0.0003$; OR = 4.01, 95% CI, 1.87-9.12, $P = 7.8 \times 10^{-4}$), respectively; data were adjusted for age and sex). When analyzing the survival time of RCC, patients with CXCL12 rs1801157AA genotype revealed significantly shorter survival time compared to cases with CXCL12 rs1801157GG and GA genotypes ($P = 0.001$), whereas RCC patients carrying CXCR4 rs2228014CT and TT genotypes showed shorter survival time than the wild type ($P = 0.002$). These data indicated that CXCL12 and CXCR4 may be new risk factors for RCC and could be used as prognostic markers for this malignancy.

[342]

TÍTULO / TITLE: - Knockdown of cyclophilin A reverses paclitaxel resistance in human endometrial cancer cells via suppression of MAPK kinase pathways.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep 14.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2285-8](https://doi.org/10.1007/s00280-013-2285-8)

AUTORES / AUTHORS: - Li Z; Min W; Gou J

INSTITUCIÓN / INSTITUTION: - Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, 610041, People's Republic of China, gingshanxiagu@tom.com.

RESUMEN / SUMMARY: - PURPOSE: Paclitaxel resistance remains to be a major obstacle to the chemotherapy of endometrial cancer. Using proteomic-based approach, we used to identify cyclophilin A (CypA) as a potential therapeutic target for endometrial cancer. As a natural continuation, this study aimed to reveal the correlation between CypA and paclitaxel resistance and evaluate the possibility of CypA as a therapeutic target for reversal of resistance. METHODS: Two paclitaxel-resistant endometrial cancer cell sublines HEC-1-B/TAX and AN3CA/TAX were generated, and expressions of CypA, P-gp, MRP-2 and survivin were demonstrated by Western blotting. CypA was knocked down by RNA interference, and the subsequent effects on the alteration of paclitaxel resistance were examined by MTT, flow cytometry and migratory/invasive transwell assays. MAPK kinases activities were examined by Western blotting. RESULTS: CypA knockdown led to significant inhibition of cell proliferation, induction of apoptosis and suppression of migratory/invasive capacity in HEC-1-B/TAX and AN3CA/TAX cells when exposed to paclitaxel. CypA knockdown led to reductions in total and phosphorylated MAPK kinases, including Akt, ERK1/2, p38 MAPK and JNK, in HEC-1-B/TAX cells. Furthermore, pretreatment with MAPK kinase inhibitors exhibited a synergistic effect in combination with CypA knockdown. CONCLUSIONS: These results demonstrated that CypA expression was up-regulated in paclitaxel-resistant cancer cells, and knockdown of CypA could reverse the paclitaxel resistance through, at least partly, suppression of MAPK kinase pathways, presenting a possibility of CypA serving as a therapeutic target to overcome paclitaxel resistance.

[343]

TÍTULO / TITLE: - Transferrin as a drug carrier: Cytotoxicity, cellular uptake and transport kinetics of doxorubicin transferrin conjugate in the human leukemia cells.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Sep 19. pii: S0887-2333(13)00222-1. doi: 10.1016/j.tiv.2013.09.013.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.09.013](https://doi.org/10.1016/j.tiv.2013.09.013)

AUTORES / AUTHORS: - Szwed M; Matusiak A; Laroche-Clary A; Robert J; Marszalek I; Jozwiak Z

INSTITUCIÓN / INSTITUTION: - Department of Thermobiology, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143 Street, 90-236 Lodz, Poland. Electronic address: szwedma@biol.uni.lodz.pl.

RESUMEN / SUMMARY: - Leukemias are one of most common malignancies worldwide. There is a substantial need for new chemotherapeutic drugs effective against this cancer. Doxorubicin (DOX), used for treatment of leukemias and solid tumors, is poorly efficacious when it is administered systemically at conventional doses. Therefore, several strategies have been developed to reduce the side effects of this anthracycline treatment. In this study we compared the effect of DOX and doxorubicin-transferrin conjugate (DOX-TRF) on human leukemia cell lines: chronic erythromyeloblastoid leukemia (K562), sensitive and resistant (K562/DOX) to doxorubicin, and acute lymphoblastic leukemia (CCRF-CEM). Experiments were also carried out on normal cells, peripheral blood mononuclear cells (PBMC). We analyzed the chemical structure of DOX-TRF conjugate by using mass spectroscopy. The in vitro growth-inhibition assay XTT, indicated that DOX-TRF is more cytotoxic for leukemia cells sensitive and resistant to doxorubicin and significantly less sensitive to normal cells compared to DOX alone. During the assessment of intracellular DOX-TRF accumulation it was confirmed that the tested malignant cells were able to retain the examined conjugate for longer periods of time than normal lymphocytes. Comparison of kinetic parameters showed that the rate of DOX-TRF efflux was also slower in the tested cells than free DOX. The results presented here should contribute to the understanding of the differences in antitumor activities of the DOX-TRF conjugate and free drug.

[344]

TÍTULO / TITLE: - Follicle-stimulating hormone inhibits apoptosis in ovarian cancer cells by regulating the OCT4 stem cell signaling pathway.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1194-204. doi: 10.3892/ijo.2013.2054. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2054](#)

AUTORES / AUTHORS: - Zhang Z; Zhu Y; Lai Y; Wu X; Feng Z; Yu Y; Bast RC Jr; Wan X; Xi X; Feng Y

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Shanghai Jiao Tong University Affiliated First People's Hospital, Shanghai, P.R. China.

RESUMEN / SUMMARY: - OCT4, a stem cell marker, is overexpressed in several types of human cancer and can induce resistance to chemotherapy and inhibition of apoptosis. We previously demonstrated that human follicle stimulating hormone (FSH) can inhibit ovarian cancer cell apoptosis. However, the role of OCT4 in FSH-induced inhibition of apoptosis has not been reported in detail. Here, we profiled OCT4 protein expression in ovarian epithelial cancer (OEC) with benign cystadenoma, borderline tumor and carcinoma tissues as well as different ovarian cancer cell lines and normal ovarian epithelial cells. Furthermore, the effects of FSH on OCT4 expression and related signaling pathways were evaluated. The overexpression of OCT4 in ovarian

carcinoma and OEC cell lines suggest that OCT4 plays a critical role in OEC carcinogenesis. Moreover, FSH-induced apoptosis inhibition was confirmed and FSH stimulation induced the expansion of CD44+CD117+ cells with a stem cell-like phenotype. Re-expression of OCT4 enhanced the expression of Notch, Sox2 and Nanog molecules that play critical roles in cancer stem cell proliferation and differentiation. FSH upregulated the expression of Notch, Sox2 and Nanog and these effects were abolished by knocking down OCT4, suggesting that several cancer stem cell pathways are involved in FSH regulation. We also examined OCT4 expression in surgical specimens of ovarian cancer. Immunohistostaining revealed that OCT4 expression was increased in ovarian carcinoma compared with benign cystadenomas and borderline tumors, and OCT4 expression was significantly correlated with histological grade. Staining for OCT4 was increased in serous cystadenocarcinoma, when compared with clear cell carcinoma. In summary, the OCT4 cancer stem cell signaling pathway may mediate FSH-induced inhibition of apoptosis and could provide a target for treatment of ovarian cancer.

[345]

TÍTULO / TITLE: - Significance of TP53 mutations determined by next-generation “deep” sequencing in prognosis of estrogen receptor-positive breast cancer.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Aug 21. pii: S0304-3835(13)00603-4. doi: 10.1016/j.canlet.2013.08.028.

●● Enlace al texto completo (gratis o de pago) 1016/j.canlet.2013.08.028

AUTORES / AUTHORS: - Uji K; Naoi Y; Kagara N; Shimoda M; Shimomura A; Maruyama N; Shimazu K; Kim SJ; Noguchi S

INSTITUCIÓN / INSTITUTION: - Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Osaka, Japan.

RESUMEN / SUMMARY: - Next-generation “deep” sequencing (NGS) was used for the mutational analysis of TP53, and a DNA microarray was used for the determination of the TP53 mutation-associated gene expression signature (TP53 GES) in 115 estrogen receptor (ER)-positive breast cancers. NGS detected 27 TP53 mutations, of which 20 were also detected by Sanger sequencing (SS) and seven were detected only by NGS. A significantly higher number of mutant alleles (33.9%) was detected in the tumors with TP53 mutations detected by SS compared with those with TP53 mutations detected only by NGS (11.1%). The TP53 mutations detected by NGS were more significantly associated with a large tumor size, a high histological grade, progesterone receptor-negativity, and HER2-positivity compared with those detected by SS. The TP53 mutations detected by SS, but not those detected by NGS or the p53 immunohistochemistry, exhibited a significant association with poor prognosis. In addition, the TP53 GES more clearly differentiated low- from high-risk patients for

relapse than the TP53 mutations detected by SS, regardless of the other conventional prognostic factors. Thus, NGS is more sensitive for the detection of TP53 mutations, but the prognostic significance of these mutations could not be demonstrated. In contrast, the TP53 GES proved to be a powerful prognostic indicator for ER-positive tumors.

[346]

TÍTULO / TITLE: - Interferon Therapy for Kaposi Sarcoma Associated with Acquired Immunodeficiency Syndrome: Still a Valid Treatment Option?

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

REVISTA / JOURNAL: - AIDS Patient Care STDS. 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1089/apc.2013.0184](#)

AUTORES / AUTHORS: - Rouanet I; Lechiche C; Doncesco R; Mauboussin JM; Sotto A

INSTITUCIÓN / INSTITUTION: - University Hospital of Nimes , Nimes, France .

[347]

TÍTULO / TITLE: - ADAM12 redistributes and activates MMP-14, resulting in gelatin degradation, reduced apoptosis, and increased tumor growth.

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

REVISTA / JOURNAL: - J Cell Sci. 2013 Sep 4.

●● Enlace al texto completo (gratis o de pago) [1242/jcs.129510](#)

AUTORES / AUTHORS: - Albrechtsen R; Kveiborg M; Stautz D; Vikesa J; Noer JB; Kotzsh A; Nielsen FC; Wewer U; Frohlich C

RESUMEN / SUMMARY: - Matrix metalloproteases (MMPs), in particular MMP-2, -9, and -14, play a key role in various aspects of cancer pathology. Likewise, ADAMs (A Disintegrin And Metalloproteases), including ADAM12, are upregulated in malignant tumors and contribute to the pathology of cancers. Here we showed a positive correlation between MMP-14 and ADAM12 expression in human breast cancer. We demonstrated that in 293-VnR and human breast cancer cells expressing ADAM12 at the cell surface, endogenous MMP-14 was recruited to the cell surface, resulting in its activation. Subsequent to this activation, gelatin degradation was stimulated and tumor-cell apoptosis was decreased, with reduced expression of the pro-apoptotic proteins BCL2L11 and BIK. The effect on gelatin degradation was abrogated by inhibition of the MMP-14 activity and appeared to be dependent on cell-surface alphaVbeta3 integrin localization, but neither the catalytic activity of ADAM12 nor the cytoplasmic tail of ADAM12 were required. The significance of ADAM12-induced activation of MMP-14 was underscored by a reduction in MMP-14-mediated gelatin degradation and abolition of apoptosis-protective effects by specific monoclonal antibodies against ADAM12. Furthermore, orthotopic implantation of ADAM12-

expressing MCF7 cells in nude mice produced tumors with increased levels of activated MMP-14 and confirmed that ADAM12 protects tumor cells against apoptosis, leading to increased tumor progression. In conclusion, our data suggest that a ternary protein complex composed of ADAM12, alphaVbeta3 integrin, and MMP-14 at the tumor cell surface regulates MMP-14 functions. This interaction may point to a novel concept for the development of MMP-14-targeting drugs in treating cancer.

[348]

TÍTULO / TITLE: - Phospholipase D inhibitor enhances radiosensitivity of breast cancer cells.

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

REVISTA / JOURNAL: - Exp Mol Med. 2013 Aug 30;45:e38. doi: 10.1038/emm.2013.75.

●● Enlace al texto completo (gratis o de pago) [1038/emm.2013.75](#)

AUTORES / AUTHORS: - Cheol Son J; Woo Kang D; Mo Yang K; Choi KY; Gen Son T; Min do S

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology, College of Natural Science, Pusan National University, Busan, Republic of Korea.

RESUMEN / SUMMARY: - Radiation and drug resistance remain the major challenges and causes of mortality in the treatment of locally advanced, recurrent and metastatic breast cancer. Dysregulation of phospholipase D (PLD) has been found in several human cancers and is associated with resistance to anticancer drugs. In the present study, we evaluated the effects of PLD inhibition on cell survival, cell death and DNA damage after exposure to ionizing radiation (IR). Combined IR treatment and PLD inhibition led to an increase in the radiation-induced apoptosis of MDA-MB-231 metastatic breast cancer cells. The selective inhibition of PLD1 and PLD2 led to a significant decrease in the IR-induced colony formation of breast cancer cells. Moreover, PLD inhibition suppressed the radiation-induced activation of extracellular signal-regulated kinase and enhanced the radiation-stimulated phosphorylation of the mitogen-activated protein kinases p38 and c-Jun N-terminal kinase. Furthermore, PLD inhibition, in combination with radiation, was very effective at inducing DNA damage, when compared with radiation alone. Taken together, these results suggest that PLD may be a useful target molecule for the enhancement of the radiotherapy effect.

[349]

TÍTULO / TITLE: - SIRT3 regulates cell proliferation and apoptosis related to energy metabolism in non-small cell lung cancer cells through deacetylation of NMNAT2.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1420-30. doi: 10.3892/ijo.2013.2103. Epub 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) 3892/ijo.2013.2103

AUTORES / AUTHORS: - Li H; Feng Z; Wu W; Li J; Zhang J; Xia T

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Air Force General Hospital, Beijing 100142, P.R. China.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of death worldwide and associated with dismal prognoses. As a major mitochondrial deacetylase, SIRT3 regulates the activity of enzymes to coordinate global shifts in cellular metabolism and has important implications for tumor growth. Its role as a tumor suppressor or an oncogene in lung cancer is unclear, especially in non-small cell lung carcinoma (NSCLC). To identify the mechanism of SIRT3-interacting proteins, we performed a yeast two-hybrid screen using a human lung cDNA library. One of the positive clones encoded the full-length cDNA of the nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2) gene and the interaction between SIRT3 and NMNAT2 was identified. The interaction on growth, proliferation, apoptosis of NSCLC cell lines, and energy metabolism related to SIRT3 were investigated. Screening from the library resulted in NMNAT2 gene. We found that NMNAT2 interacts with SIRT3 both in vitro and in vivo; SIRT3 binds to NMNAT2 deacetylating it. Downregulation of SIRT3 inhibited acetylation of NMNAT2 and NAD⁺ synthesis activity of the enzyme. Low expression of SIRT3 significantly inhibited mitotic entry, growth and proliferation of NSCLC cell lines and promoted apoptosis, which was related to energy metabolism involving in the interaction between SIRT3 and NMNAT2. Taken together, our results strongly suggest that the binding of SIRT3 with NMNAT2 is a novel regulator of cell proliferation and apoptosis in NSCLC cell lines, implicating the interaction between SIRT3 and NMNAT2, energy metabolism associated with SIRT3.

[350]

TÍTULO / TITLE: - Molecular Pathways and Functional Analysis of miRNA Expression Associated with Paclitaxel-Induced Apoptosis in Hepatocellular Carcinoma Cells.

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

REVISTA / JOURNAL: - Pharmacology. 2013 Sep 20;92(3-4):167-174.

●● Enlace al texto completo (gratis o de pago) 1159/000354585

AUTORES / AUTHORS: - Yan H; Wang S; Yu H; Zhu J; Chen C

INSTITUCIÓN / INSTITUTION: - National Engineering Research Center for Miniaturized Detection System, College of Life Sciences, Northwest University, Xi'an, China.

RESUMEN / SUMMARY: - Background: We postulated that microRNAs (miRNAs) might be involved in hepatocellular carcinoma (HCC) targeted chemotherapy with paclitaxel. This study sought to generate a list of potential miRNA-based biomarkers and their potential targets to better understand the response to paclitaxel treatment in HCC. Methods: Cell viability proliferation assays were conducted to test the sensitivity of the HepG2 cells to paclitaxel. The morphological changes of apoptosis were assessed with

4',6-diamidino-2-phenylindole staining. Differential expression patterns of miRNA in the HepG2 cells either treated or not treated were analyzed using miRNA microarrays. Results: The array experiments have identified 54 miRNAs whose basal expression levels differed by >2-fold and $p < 0.05$ between the two phenotypic groups. The data were validated by a quantitative real-time PCR of 8 selected miRNAs (miR-21, miR-1274^a, miR-1260, miR-1290, miR-508-5p, miR-877, miR-1246, miR-183*). The PI3K/Akt, mitogen-activated protein kinase (MAPK), TGF-beta, ErbB, p53, cell cycle, mammalian target of rapamycin, and Jak-STAT signaling pathways were involved in paclitaxel-induced apoptosis. Conclusions: The manipulation of one or more of these miRNAs could be an important approach for the improved management of paclitaxel therapy. © 2013 S. Karger AG, Basel.

[351]

TÍTULO / TITLE: - Sodium butyrate inhibits interferon-gamma induced indoleamine 2,3-dioxygenase expression via STAT1 in nasopharyngeal carcinoma cells.

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

REVISTA / JOURNAL: - Life Sci. 2013 Oct 10;93(15):509-515. doi: 10.1016/j.lfs.2013.07.028. Epub 2013 Aug 11.

●● Enlace al texto completo (gratis o de pago) 1016/j.lfs.2013.07.028

AUTORES / AUTHORS: - He YW; Wang HS; Zeng J; Fang X; Chen HY; Du J; Yang XY

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou 510120, China. Electronic address: heyuwen82@126.com.

RESUMEN / SUMMARY: - AIMS: Indoleamine 2,3-dioxygenase (IDO) inhibits T-cell proliferation by catalyzing the conversion of l-tryptophan to l-kynurenine. IDO-induced immune tolerance weakens the clinical outcomes of immunotherapies. Sodium butyrate (NaB), one of the histone deacetylase inhibitors (HDACIs), has potential anti-tumor effects. Our previous studies revealed that NaB could inhibit IFN-gamma induced IDO expression in nasopharyngeal carcinoma cells, CNE2. In the present study, we aim to investigate to the mechanism of NaB interfering with the interferon-gamma (IFN-gamma)-mediated IDO expression signaling transduction. MAIN METHODS: IDO expression and STAT1 phosphorylation in CNE2 cells were analyzed by western blotting and STAT1 acetylation was evaluated by immunoprecipitation. STAT1 nuclear translocation and NF-kappaB activity were detected by transient transfection and reporter gene assay. KEY FINDINGS: We found that NaB inhibited IFN-gamma-induced IDO expression in CNE2 cells via decreasing phosphorylation and nuclear translocation of STAT1, but not via down-regulation of IFN-gamma-receptor (IFNGR). Immunoprecipitation assays revealed that NaB increased STAT1 acetylation. Furthermore, NaB elevated the activity of NF-kappaB in CNE2 cells, and blocking the NF-kappaB activity had no effect on the IFN-gamma-induced IDO expression.

SIGNIFICANCE: These results suggest that NaB inhibited IFN-gamma-induced IDO expression via STAT1 increased acetylation, decreased phosphorylation, and reduced nuclear translocation. These provided new evidence for the anti-tumor action of NaB and potential drug targets to reduce the IDO-induced immune tolerance.

[352]

TÍTULO / TITLE: - Differential Response to Neoadjuvant Chemotherapy Among 7 Triple-Negative Breast Cancer Molecular Subtypes.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5533-5540. Epub 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0799](#)

AUTORES / AUTHORS: - Masuda H; Baggerly KA; Wang Y; Zhang Y; Gonzalez-Angulo AM; Meric-Bernstam F; Valero V; Lehmann BD; Pietersen JA; Hortobagyi GN; Symmans WF; Ueno NT

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Morgan Welch Inflammatory Breast Cancer Research Program and Clinic; Departments of Breast Medical Oncology, Bioinformatics and Computational Biology, Pathology, and Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; and Department of Biochemistry, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee.

RESUMEN / SUMMARY: - PURPOSE: The clinical relevancy of the 7-subtype classification of triple-negative breast cancer (TNBC) reported by Lehmann and colleagues is unknown. We investigated the clinical relevancy of TNBC heterogeneity by determining pathologic complete response (pCR) rates after neoadjuvant chemotherapy, based on TNBC subtypes. EXPERIMENTAL DESIGN: We revalidated the Lehmann and colleagues experiments using Affymetrix CEL files from public datasets. We applied these methods to 146 patients with TNBC with gene expression microarrays obtained from June 2000 to March 2010 at our institution. Of those, 130 had received standard neoadjuvant chemotherapy and had evaluable pathologic response data. We classified the TNBC samples by subtype and then correlated subtype and pCR status using Fisher exact test and a logistic regression model. We also assessed survival and compared the subtypes with PAM50 intrinsic subtypes and residual cancer burden (RCB) index. RESULTS: TNBC subtype and pCR status were significantly associated ($P = 0.04379$). The basal-like 1 (BL1) subtype had the highest pCR rate (52%); basal-like 2 (BL2) and luminal androgen receptor had the lowest (0% and 10%, respectively). TNBC subtype was an independent predictor of pCR status ($P = 0.022$) by a likelihood ratio test. The subtypes better predicted pCR status than did the PAM50 intrinsic subtypes (basal-like vs. non basal-like). CONCLUSIONS: Classifying TNBC by 7 subtypes predicts high versus low pCR rate. We confirm the clinical relevancy of the 7 subtypes of TNBC. We need to prospectively validate whether the

pCR rate differences translate into long-term outcome differences. The 7-subtype classification may spur innovative personalized medicine strategies for patients with TNBC. Clin Cancer Res; 19(19); 5533-40. ©2013 AACR.

[353]

TÍTULO / TITLE: - Mucin expression in gastric cancer: reappraisal of its clinicopathologic and prognostic significance.

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

REVISTA / JOURNAL: - Arch Pathol Lab Med. 2013 Aug;137(8):1047-53. doi: 10.5858/arpa.2012-0193-OA.

●● Enlace al texto completo (gratis o de pago) [5858/arpa.2012-0193-OA](#)

AUTORES / AUTHORS: - Kim DH; Shin N; Kim GH; Song GA; Jeon TY; Kim DH; Lauwers GY; Park do Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Pusan National University Hospital, Busan, Korea.

RESUMEN / SUMMARY: - CONTEXT: The clinical validity of mucin expression in gastric cancer is debated. Whereas several reports demonstrate a correlation between mucin expression and prognosis, others deny such an association. OBJECTIVES: This survival analysis study aims to elucidate the prognostic significance of mucin expression in gastric cancer. DESIGN: A retrospective survival analysis was done with 412 cases of gastric cancer characterized on the basis of MUC immunohistochemistry using MUC2, MUC5AC, MUC6, and CD10 antibodies; the cases were divided into those with a gastric, an intestinal, or a null mucin phenotype based on the predominant mucin. RESULTS: There was no association between mucin expression and survival when considering overall gastric cancers or the advanced gastric cancer subtype. However, early gastric cancers with a gastric mucin phenotype showed longer survival than those with an intestinal mucin phenotype (P = .01) or a null phenotype (P = .01). In particular, MUC5AC-positive early gastric cancers resulted in longer survival than did those that did not express MUC5AC (P = .009). The loss of MUC5AC expression was identified as an independent, poor prognostic factor in early gastric cancers using the Cox regression proportional hazard model (hazard ratio, 3.50; P = .045). CONCLUSIONS: MUC5AC expression is significantly associated with patient survival and can be used to predict outcomes in the gastric cancers, especially in the early gastric cancers.

[354]

TÍTULO / TITLE: - Capsaicin induces apoptosis in human osteosarcoma cells through AMPK-dependent and AMPK-independent signaling pathways.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1802-8](https://doi.org/10.1007/s11010-013-1802-8)

AUTORES / AUTHORS: - Ying H; Wang Z; Zhang Y; Yang TY; Ding ZH; Liu SY; Shao J; Liu Y; Fan XB

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Gongli Hospital of Pudong New District, No. 219, Miaopu Road, Pudong New District, Shanghai, 200135, China.

RESUMEN / SUMMARY: - Recent studies have focused on the anti-tumor activity of capsaicin. However, the potential effects of capsaicin in osteosarcoma cells and the underlying mechanisms are not fully understood. In the current study, we observed that capsaicin-induced growth inhibition and apoptosis in cultured osteosarcoma cells (U2OS and MG63), which were associated with a significant AMP-activated protein kinase (AMPK) activation. AMPK inhibition by compound C or RNA interference suppressed capsaicin-induced cytotoxicity, while AMPK activators (AICAR and A769662) promoted osteosarcoma cell death. For the mechanism study, we found that AMPK activation was required for capsaicin-induced mTORC1 (mTOR complex 1) inhibition, B cell lymphoma 2 (Bcl-2) downregulation and Bax upregulation in MG63 cells. Capsaicin administration induced p53 activation, mitochondrial translocation and Bcl-2 killer association, such effects were dependent on AMPK activation. Interestingly, we observed a significant pro-apoptotic c-Jun NH2-terminal kinases activation by capsaicin in MG63 cells, which appeared to be AMPK independent. In conclusion, capsaicin possessed strong efficacy against human osteosarcoma cells. Molecular studies revealed that capsaicin activated AMPK-dependent and AMPK-independent signalings to mediate cell apoptosis. The results of this study should have significant translational relevance in managing this deadly malignancy.

[355]

TÍTULO / TITLE: - Ethanol induces cell cycle arrest and triggers apoptosis via Sp1-dependent p75NTR expression in human neuroblastoma cells.

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

REVISTA / JOURNAL: - Cell Biol Toxicol. 2013 Oct;29(5):365-80. doi: 10.1007/s10565-013-9260-3. Epub 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1007/s10565-013-9260-3](https://doi.org/10.1007/s10565-013-9260-3)

AUTORES / AUTHORS: - Do H; Park HJ; Sohn EH; Kim BO; Um SH; Kwak JH; Moon EY; Rhee DK; Pyo S

INSTITUCIÓN / INSTITUTION: - School of Medicine, Tan Tao University, Tan Duc ECity, Long An Province, Viet Nam.

RESUMEN / SUMMARY: - Ethanol exposure has deleterious effects on the central nervous system. Although several mechanisms for ethanol-induced damage have been suggested, the precise mechanism underlying ethanol-induced neuronal cell death remains unclear. Recent studies indicate that the p75 neurotrophin receptor (p75NTR) has a critical role in the regulation of neuronal survival. This study was designed to

examine the role of p75NTR in ethanol-induced apoptotic signaling in neuroblastoma cells. Ethanol caused highly increased level of p75NTR expression. The use of small interfering RNA to inhibit p75NTR expression markedly attenuated ethanol-induced cell cycle arrest and apoptosis. DNA binding activity of Sp1 was increased by ethanol, whereas inhibition of Sp1 activity by mithramycin, a Sp1 inhibitor, or short hairpin RNA suppressed ethanol-induced p75NTR expression. In addition, inhibitors of casein kinase 2 (CK2) and extracellular signal-regulated kinase (ERK) augmented ethanol-induced p75NTR expression. Our results also demonstrate that inhibition of ERK and CK2 caused a further increase in the activation of the p75NTR proximal promoter induced by ethanol. This increased activation was partially suppressed by the deletion of the Sp1 binding sites. These results suggest that Sp1-mediated p75NTR expression is regulated at least in part by ERK and CK2 pathways. The present study also showed that treatment with ethanol resulted in significant increases in the expression of p21, but not the levels of p53 and p53 target genes such as Bax, Puma, and Bcl-2. Furthermore, the inhibition of p75NTR expression or Sp1 activity suppressed ethanol-induced p21 expression, cell cycle arrest, and apoptosis. These data suggest that ethanol increases p75NTR expression, and CK2 and ERK signaling inversely regulate Sp1-mediated p75NTR expression in ethanol-treated neuroblastoma cells. Thus, our study provides more insight into the mechanisms underlying ethanol actions.

[356]

TÍTULO / TITLE: - Predictive factors for early and late local toxicities in anal cancer treated by radiotherapy in combination with or without chemotherapy.

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

REVISTA / JOURNAL: - Dis Colon Rectum. 2013 Oct;56(10):1125-33. doi: 10.1097/DCR.0b013e3182a226bd.

●● Enlace al texto completo (gratis o de pago) [1097/DCR.0b013e3182a226bd](#)

AUTORES / AUTHORS: - Doyen J; Benezery K; Follana P; Ortholan C; Gerard JP; Hannoun-Levi JM; Gal J; Francois E

INSTITUCIÓN / INSTITUTION: - 1 Department of Radiation Oncology, Centre Antoine-Lacassagne, Nice, France 2 Department of Medical Oncology, Centre Antoine-Lacassagne, Nice, France 3 Department of Medical Statistics, Centre Antoine-Lacassagne, Nice, France.

RESUMEN / SUMMARY: - BACKGROUND: The treatment of anal cancer is based on concomitant radiotherapy and chemotherapy and is associated with a nonnegligible rate of local severe toxicities that can strongly impair the quality of life. OBJECTIVE: A retrospective analysis was performed to screen the following factors as potential predictive factors for local skin and digestive toxicities, and as potential prognostic factors for cumulative colostomy incidence: sex, age, tumor size, clinical T and N stage, circumferential extension, invasion of anal margin, HIV status, type of chemotherapy,

and type of radiotherapy and dose delivered. METHODS: One hundred five patients in our database treated between January 2000 and February 2010 met the eligibility criteria. RESULTS: Median follow-up was 54.1 months (range, 1-133). Early and late severe local toxicities occurred in 33 patients (31.4%) and 18 patients (17.1%). The 5-year cumulative rate of colostomy was 26.6%. Predictive factors for local severe early toxicities were as follows: clinical stage III/IV ($p = 0.01$), no brachytherapy boost ($p = 0.003$), and use of chemotherapy ($p = 0.01$). Only brachytherapy retained its independence in multivariate analysis (OR = 4.8 (1.4-16.3), $p = 0.01$). Human immunodeficiency virus positivity ($p = 0.04$) was the only predictive factor for late toxicities in univariate analysis; it was linked independently to the occurrence of ulcer (OR = 0.1 (0.01-0.66), $p = 0.01$). Tumor size ≥ 4 cm ($p < 0.001$) and occurrence of grade 2 to 3 ulcers ($p < 0.001$) were correlated with greater cumulative colostomy incidence. CONCLUSIONS: In this cohort, nonuse of brachytherapy was an independent predictive factor for local acute toxicity. Human immunodeficiency virus positivity was the only predictive factor for local late toxicities and strongly influenced the onset of ulcer.

[357]

TÍTULO / TITLE: - A rare case of lymphangiomyomatosis treated with leuprolide acetate: five-years follow-up.

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

REVISTA / JOURNAL: - Eur J Gynaecol Oncol. 2013;34(3):278-9.

AUTORES / AUTHORS: - Bastu E; Akhan SE; Karamustafaoglu B; Gungor-Ugurlucan F; Sozen H; Iyibozkurt AC

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Istanbul University School of Medicine, Istanbul, Turkey. ercan.bastu@istanbul.edu.tr

RESUMEN / SUMMARY: - Lymphangiomyomatosis (LAM) is a rare and systemic disease that is characterized by the abnormal proliferation of smooth muscle-like cells in the lungs and along the axial lymphatic system. The authors herein present a rare case of LAM that was treated with long-term use of leuprolide acetate, a gonadotropin-releasing hormone analogue (GnRHa).

[358]

TÍTULO / TITLE: - Combination of two anti-CD5 monoclonal antibodies synergistically induces complement-dependent cytotoxicity of chronic lymphocytic leukaemia cells.

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

REVISTA / JOURNAL: - Br J Haematol. 2013 Aug 8. doi: 10.1111/bjh.12503.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12503](https://doi.org/10.1111/bjh.12503)

AUTORES / AUTHORS: - Klitgaard JL; Koefoed K; Geisler C; Gadeberg OV; Frank DA; Petersen J; Jurlander J; Pedersen MW

INSTITUCIÓN / INSTITUTION: - Symphogen A/S, Lyngby, Denmark; Department of Haematology L4042, Rigshospitalet, Copenhagen.

RESUMEN / SUMMARY: - The treatment of chronic lymphocytic leukaemia (CLL) has been improved by introduction of monoclonal antibodies (mAbs) that exert their effect through secondary effector mechanisms. CLL cells are characterized by expression of CD5 and CD23 along with CD19 and CD20, hence anti-CD5 Abs that engage secondary effector functions represent an attractive opportunity for CLL treatment. Here, a repertoire of mAbs against human CD5 was generated and tested for ability to induce complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) both as single mAbs and combinations of two mAbs against non-overlapping epitopes on human CD5. The results demonstrated that combinations of two mAbs significantly increased the level of CDC compared to the single mAbs, while no enhancement of ADCC was seen with anti-CD5 mAb combinations. High levels of CDC and ADCC correlated with low levels of Ab-induced CD5 internalization and degradation. Importantly, an anti-CD5 mAb combination enhanced CDC of CLL cells when combined with the anti-CD20 mAbs rituximab and ofatumumab as well as with the anti-CD52 mAb alemtuzumab. These results suggest that an anti-CD5 mAb combination inducing CDC and ADCC may be effective alone, in combination with mAbs against other targets or combined with chemotherapy for CLL and other CD5-expressing haematological or lymphoid malignancies.

[359]

TÍTULO / TITLE: - SL-01, an oral derivative of gemcitabine, inhibited human breast cancer growth through induction of apoptosis.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Aug 23;438(2):402-9. doi: 10.1016/j.bbrc.2013.07.087. Epub 2013 Jul 27.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bbrc.2013.07.087](#)

AUTORES / AUTHORS: - Li YY; Qin YZ; Wang RQ; Li WB; Qu XJ

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, China.

RESUMEN / SUMMARY: - SL-01 is an oral derivative of gemcitabine that was synthesized by introducing the moiety of 3-(dodecyloxycarbonyl) pyrazine-2-carbonyl at N4-position on cytidine ring of gemcitabine. We aimed to evaluate the efficacy of SL-01 on human breast cancer growth. SL-01 significantly inhibited MCF-7 proliferation as estimated by colorimetric assay. Flow cytometry assay indicated the apoptotic induction and cell cycle arrest in G1 phase. SL-01 modulated the expressions of p-ATM, p53 and p21 and decrease of cyclin D1 in MCF-7 cells. Further experiments were

performed in a MCF-7 xenografts mouse model. SL-01 by oral administration strongly inhibited MCF-7 xenografts growth. This effect of SL-01 might arise from its roles in the induction of apoptosis. Immunohistochemistry assay showed the increase of TUNEL staining cells. Western blotting indicated the modulation of apoptotic proteins in SL-01-treated xenografts. During the course of study, there was no evidence of toxicity to mice. In contrast, the decrease of neutrophil cells in peripheral and increase of AST and ALT levels in serum were observed in the gemcitabine-treated mice. Conclusion: SL-01 possessed similar activity against human breast cancer growth with gemcitabine, whereas, with lower toxicity to gemcitabine. SL-01 is a potent oral agent that may supplant the use of gemcitabine.

[360]

TÍTULO / TITLE: - Erratum to: Identification of differentially expressed proteins in chemotherapy-sensitive and chemotherapy-resistant diffuse large B cell lymphoma by proteomic methods.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):672. doi: 10.1007/s12032-013-0672-y.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0672-y](#)

AUTORES / AUTHORS: - Liu Y; Zeng L; Zhang S; Zeng S; Huang J; Tang Y; Zhong M

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Xiangya Hospital, Central South University, 88 Xiangya Road, Changsha, 410008, Hunan, People's Republic of China.

[361]

TÍTULO / TITLE: - OSU-A9, an indole-3-carbinol derivative, induces cytotoxicity in acute myeloid leukemia through reactive oxygen species-mediated apoptosis.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Sep 13. pii: S0006-2952(13)00573-X. doi: 10.1016/j.bcp.2013.09.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.09.002](#)

AUTORES / AUTHORS: - Bai LY; Weng JR; Chiu CF; Wu CY; Yeh SP; Sargeant AM; Lin PH; Liao YM

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, 2, Yude road, Taichung 40402 Taiwan; College of Medicine, School of Medicine, China Medical University, 91, Hsueh-Shih road, Taichung 40402 Taiwan. Electronic address: lybai6@gmail.com.

RESUMEN / SUMMARY: - Indole-3-carbinol (I3C) is a broadly targeted phytochemical shown to prevent carcinogenesis in animal studies and to suppress the proliferation of cancer cells of human breast, colon, prostate, and endometrium. Here we demonstrate that OSU-A9, an I3C derivative with improved anticancer potency,

induces cytotoxicity in acute myeloid leukemia (AML) cell lines (HL-60 and THP-1) and primary leukemia cells from AML patients in a dose-responsive manner. Normal human bone marrow cells were less sensitive to OSU-A9 than leukemia cells. OSU-A9 induces caspase activation, PARP cleavage, and autophagy but not autophagic cell death. Interestingly, pretreatment of AML cell lines and primary AML cells with N-acetylcysteine or glutathione rescues them from apoptosis (and concomitant PARP cleavage) and Akt hypophosphorylation, implicating a key role of reactive oxygen species (ROS) in OSU-A9-related cytotoxicity. Importantly, the anticancer utility of OSU-A9 is extended in vivo as it, administered intraperitoneally, suppresses the growth of THP-1 xenograft tumors in athymic nude mice without obvious toxicity. This study shows that ROS-mediated apoptosis contributes to the anticancer activity of OSU-A9 in AML cell lines and primary AML cells, and thus should be considered in the future assessment of its translational value in AML therapy.

[362]

TÍTULO / TITLE: - Renal Tumors: Diagnostic and Prognostic Biomarkers.

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

REVISTA / JOURNAL: - Am J Surg Pathol. 2013 Oct;37(10):1518-1531.

●● [Enlace al texto completo \(gratis o de pago\) 1097/PAS.0b013e318299f12e](#)

AUTORES / AUTHORS: - Tan PH; Cheng L; Rioux-Leclercq N; Merino MJ; Netto G; Reuter VE; Shen SS; Grignon DJ; Montironi R; Egevad L; Srigley JR; Delahunt B; Moch H

INSTITUCIÓN / INSTITUTION: - *Department of Pathology, Singapore General Hospital, Singapore, Singapore daggerDepartment of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN section signLaboratory of Pathology, National Cancer Institute, Bethesda parallelDepartment of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD paragraph signMemorial Sloan Kettering Cancer Center, New York, NY #Department of Pathology and Genomic Medicine, The Methodist Hospital and Weill Medical College of Cornell University, Houston, TX double daggerService d'Anatomie et Cytologie Pathologiques, CHU Pontchaillou, Rennes, France **Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region, Ancona, Italy daggerdaggerKarolinska Institute, Stockholm, Sweden double daggerdouble daggerDepartment of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada section sign section signDepartment of Pathology and Molecular Medicine, University of Otago, Wellington, New Zealand parallel parallelInstitute of Surgical Pathology, University of Zurich, Zurich, Switzerland.

RESUMEN / SUMMARY: - The International Society of Urological Pathology convened a consensus conference on renal cancer, preceded by an online survey, to address issues relating to the diagnosis and reporting of renal neoplasia. In this report, the role of biomarkers in the diagnosis and assessment of prognosis of renal tumors is addressed.

In particular we focused upon the use of immunohistochemical markers and the approach to specific differential diagnostic scenarios. We enquired whether cytogenetic and molecular tools were applied in practice and asked for views on the perceived prognostic role of biomarkers. Both the survey and conference voting results demonstrated a high degree of consensus in participants' responses regarding prognostic/predictive markers and molecular techniques, whereas it was apparent that biomarkers for these purposes remained outside the diagnostic realm pending clinical validation. Although no individual antibody or panel of antibodies reached consensus for classifying renal tumors, or for confirming renal metastatic disease, it was noted from the online survey that 87% of respondents used immunohistochemistry to subtype renal tumors sometimes or occasionally, and a majority (87%) used immunohistochemical markers (Pax 2 or Pax 8, renal cell carcinoma [RCC] marker, panel of pan-CK, CK7, vimentin, and CD10) in confirming the diagnosis of metastatic RCC. There was consensus that immunohistochemistry should be used for histologic subtyping and applied before reaching a diagnosis of unclassified RCC. At the conference, there was consensus that TFE3 and TFEB analysis ought to be requested when RCC was diagnosed in a young patient or when histologic appearances were suggestive of the translocation subtype; whereas Pax 2 and/or Pax 8 were considered to be the most useful markers in the diagnosis of a renal primary.

[363]

TÍTULO / TITLE: - Somatic Mutations in MAP3K5 Attenuate its Pro-Apoptotic Function in Melanoma Through Increased Binding to Thioredoxin.

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

REVISTA / JOURNAL: - J Invest Dermatol. 2013 Sep 5. doi: 10.1038/jid.2013.365.

●● [Enlace al texto completo \(gratis o de pago\) 1038/jid.2013.365](#)

AUTORES / AUTHORS: - Prickett TD; Zerlanko B; Gartner JJ; Parker SC; Dutton-Regester K; Lin JC; Teer JK; Wei X; Jiang J; Chen G; Davies MA; Gershenwald JE; Robinson W; Robinson S; Hayward NK; Rosenberg SA; Margulies EH; Samuels Y

INSTITUCIÓN / INSTITUTION: - The Cancer Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA.

RESUMEN / SUMMARY: - Patients with advanced metastatic melanoma have poor prognosis and the genetics underlying its pathogenesis are poorly understood. High throughput sequencing has allowed comprehensive discovery of somatic mutations in cancer samples. Here, upon analysis of our whole-genome and whole-exome sequencing data of 29 melanoma samples we identified several genes that harbor recurrent non-synonymous mutations. These included MAP3K5, which in a prevalence screen of 288 melanomas was found to harbor a R256C substitution in 5 cases. All MAP3K5 mutated samples were wild-type for BRAF, suggesting a mutual exclusivity for these mutations. Functional analysis of the MAP3K5 R256C mutation revealed

attenuation of MKK4 activation through increased binding of the inhibitory protein thioredoxin (TXN/TRX-1/Trx); resulting in increased proliferation and anchorage-independent growth of melanoma cells. This mutation represents a potential target for the design of new therapies to treat melanoma. *Journal of Investigative Dermatology* accepted article preview online, 5 September 2013. doi:10.1038/jid.2013.365.

[364]

TÍTULO / TITLE: - S100A4 mRNA expression level is a predictor of radioresistance of pancreatic cancer cells.

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

REVISTA / JOURNAL: - *Oncol Rep.* 2013 Oct;30(4):1601-8. doi: 10.3892/or.2013.2636. Epub 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2636](#)

AUTORES / AUTHORS: - Kozono S; Ohuchida K; Ohtsuka T; Cui L; Eguchi D; Fujiwara K; Zhao M; Mizumoto K; Tanaka M

INSTITUCIÓN / INSTITUTION: - Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

RESUMEN / SUMMARY: - Improving poor outcomes in patients with pancreatic cancer requires a greater understanding of the biological mechanisms contributing to radioresistance. We, therefore, sought to identify genes involved in the radioresistance of pancreatic cancer cells. Two pancreatic cancer cell lines, CFPAC-1 and Capan-1, were repeatedly exposed to radiation, establishing two radioresistant cell lines. Gene expression profiling using cDNA microarrays was performed to identify genes responsible for radioresistance. The levels of expression of mRNAs encoded by selected genes and their correlation with radiation dose resulting in 50% survival rate were analyzed in pancreatic cancer cell lines. The radiation dose resulting in a 50% survival rate was significantly higher in irradiated (IR) compared to parental CFPAC-1 cells (8.31±0.85 Gy vs. 2.14±0.04 Gy, P<0.0001), but was lower in IR compared with parental Capan-1 cells (2.66±0.24 Gy vs. 2.25±0.03 Gy, P=0.04). cDNA microarray analysis identified 4 genes, including S100 calcium binding protein A4 (S100A4), overexpressed and 23 genes underexpressed in the IR compared with the parental cell lines. The levels of S100A4 mRNA expression were correlated with radiation dose resulting in a 50% survival rate (Pearson's test, R²=0.81, P=0.0025). S100A4 mRNA expression may predict radioresistance of pancreatic cancer cells and may play an important role in the poor response of pancreatic cancer cells to radiation therapy.

[365]

TÍTULO / TITLE: - Ubiquitin-specific protease 22: a novel molecular biomarker in cervical cancer prognosis and therapeutics.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1121-4](#)

AUTORES / AUTHORS: - Yang M; Liu YD; Wang YY; Liu TB; Ge TT; Lou G

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, The Third Affiliated (Tumor) Hospital, Harbin Medical University, Harbin, 150081, China.

RESUMEN / SUMMARY: - Ubiquitin-specific protease 22 (USP22) exhibits an important function in tumor progression and oncogenesis. The aim of this study was to investigate the role of USP22 and the association with its potential targets in patients with cervical cancer. To our knowledge, this is the first study that determines the relationship between USP22 expression and clinicopathological significance in cervical cancer. The immunohistochemistry results showed that USP22 protein was overexpressed in cervical cancer samples compared with normal cervical tissues ($P < 0.001$). Moreover, clinicopathological analysis showed that USP22 expression was highly related to International Federation of Gynecology and Obstetrics stage, Ki67, lymph node metastasis, and histology grade. The results of Kaplan-Meier analysis indicated that patients with high USP22 expression had significantly shorter overall survival (OS) and disease-free survival (DFS) than patients with low expression of USP22 ($P < 0.001$). Multivariate Cox regression analysis revealed that USP22 expression status was an independent prognostic marker for both OS and DFS of patients with cervical cancer. It is suggested that USP22 overexpression may be associated with poor prognosis in cervical cancer. It may represent a novel prognostic biomarker or a target for improving the treatment efficiency of patients with cervical cancer.

[366]

TÍTULO / TITLE: - MicroRNA-29^a induces resistance to gemcitabine through the Wnt/beta-catenin signaling pathway in pancreatic cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1066-72. doi: 10.3892/ijo.2013.2037. Epub 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2037](#)

AUTORES / AUTHORS: - Nagano H; Tomimaru Y; Eguchi H; Hama N; Wada H; Kawamoto K; Kobayashi S; Doki Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan.

RESUMEN / SUMMARY: - Although we studied previously the mechanisms of resistance of pancreatic cancer cells to gemcitabine (GEM), prediction of the response to GEM remains unsatisfactory. The aim of this study was to investigate the relationship between miR-29^a expression and the response to GEM in pancreatic cancer cells. Changes in the growth-inhibitory effect of pancreatic cancer cells (MIAPaCa-2, PSN-1,

BxPC-3 and Panc-1) to GEM were examined after overexpression or suppression of miR-29^a. We also examined the effect of miR-29^a on the Wnt/beta-catenin signaling pathway and investigated whether the altered growth-inhibitory effect by miR-29^a suppression was weakened after the addition of Wnt3a, a Wnt/beta-catenin signaling activator. MIAPaCa-2 and PSN-1 cells transfected with anti-miR-29^a showed significantly lower resistance to GEM. In the anti-miR-29^a-transfected cells, GEM induced significantly larger numbers of apoptotic cells and S phase accumulation compared to control cells, demonstrated by Annexin V assay and flow cytometric analysis of the cell cycle, respectively. The transfected cells showed overexpression of putative target molecules including Dkk1, Kremen2 and sFRP2 and lower activation of the Wnt/beta-catenin signaling pathway. The addition of Wnt3a weakened the augmented growth-inhibitory effect of anti-miR-29^a transfection. Our findings suggest that miR-29^a expression correlates significantly with the growth-inhibitory effect of GEM and that activation of the Wnt/beta-catenin signaling pathway mediated the miR-29^a-induced resistance to GEM in pancreatic cancer cell lines.

[367]

TÍTULO / TITLE: - Cytokines from the tumor microenvironment modulate sirtinol cytotoxicity in A549 lung carcinoma cells.

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

REVISTA / JOURNAL: - Cytokine. 2013 Oct;64(1):196-207. doi: 10.1016/j.cyto.2013.07.029. Epub 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1016/j.cyto.2013.07.029](#)

AUTORES / AUTHORS: - Pal S; Shankar BS; Sainis KB

INSTITUCIÓN / INSTITUTION: - Radiation Biology & Health Sciences Division, Bio-Medical Group, Bhabha Atomic Research Centre, Modular Laboratories, Mumbai 400085, India.

RESUMEN / SUMMARY: - Cytokines in tumor microenvironment play an important role in the success or failure of molecular targeted therapies. We have chosen tumor necrosis factor alpha (TNF-alpha), TNF related apoptosis inducing ligand (TRAIL), insulin-like growth factor 1 (IGF-1) and transforming growth factor beta (TGF-beta) as representative pro-inflammatory, pro-apoptotic, anti-apoptotic and anti-inflammatory tumor derived cytokines. Analysis of Oncomine database revealed the differential expression of these cytokines in a subset of cancer patients. The effects of these cytokines on cytotoxicity of FDA approved drugs - cisplatin and taxol and inhibitors of epidermal growth factor receptor - AG658, Janus kinase - AG490 and SIRT1 - sirtinol were assessed in A549 lung cancer cells. TRAIL augmented cytotoxicity of sirtinol and IGF-1 had a sparing effect. Since TRAIL and IGF-1 differentially modulated sirtinol cytotoxicity, further studies were carried out to identify the mechanisms. Sirtinol or knockdown of SIRT1 increased the expression of death receptors DR4 and DR5 and sensitized A549 cells to TRAIL. Increased cell death in presence of TRAIL and sirtinol

was caspase independent and demonstrated classical features of necroptosis. Inhibition of iNOS increased caspase activity and switched the mode of cell death to caspase mediated apoptosis. Interestingly, sirtinol or SIRT1 knockdown did not increase IGF-1R expression. Instead, it abrogated ligand induced downregulation of IGF-1R and increased cell survival through PI3K-AKT pathway. In conclusion, these findings reveal that the tumor microenvironment contributes to modulation of cytotoxicity of drugs and that combination therapy, with agents that increase TRAIL signaling and suppress IGF-1 pathway may potentiate anticancer effect.

[368]

TÍTULO / TITLE: - Syndecan-1 overexpression is associated with nonluminal subtypes and poor prognosis in advanced breast cancer.

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

REVISTA / JOURNAL: - Am J Clin Pathol. 2013 Oct;140(4):468-74. doi: 10.1309/AJCPZ1D8CALHDXCJ.

●● Enlace al texto completo (gratis o de pago) [1309/AJCPZ1D8CALHDXCJ](#)

AUTORES / AUTHORS: - Nguyen TL; Grizzle WE; Zhang K; Hameed O; Siegal GP; Wei S

INSTITUCIÓN / INSTITUTION: - Dept of Pathology, University of Alabama at Birmingham, NP 3542, 619 19th St, South Birmingham, AL 35249-7331; swei@uab.edu.

RESUMEN / SUMMARY: - Objectives: Syndecan-1 expression is decreased in diverse tumor types but remains controversial in breast carcinomas. The goal of the study was to examine syndecan-1 expression in breast carcinoma and its prognostic significance. Methods: The epithelial expression of syndecan-1 was examined in tissue microarrays constructed from 62 consecutive breast carcinoma cases diagnosed between 1997 and 2004 with distant organ metastasis and 10 consecutive control cases (breast carcinoma with no distant metastasis after at least 8 years of follow-up). The prognostic significance of syndecan-1 was estimated by utilizing a Cox proportional hazards regression model. Results: Among tumors with distant metastasis, syndecan-1 expression was significantly associated with a higher histologic grade and inversely related to hormonal receptor status. The HER2 subtype and triple-negative carcinomas exhibited markedly higher syndecan-1 levels than those of luminal subtypes, while the latter remained significantly higher than nonmetastatic control cases. Furthermore, high syndecan-1 expression had a negative impact on both overall and disease-free survival rates. Conclusions: These findings suggest that syndecan-1 may regulate breast cancer cell behavior and thus deserves further investigation to ascertain its potential as a therapeutic target, especially in metastatic, triple-negative carcinomas.

[369]

TÍTULO / TITLE: - Influence of Lycopene on Cell Viability, Cell Cycle, and Apoptosis of Human Prostate Cancer and Benign Hyperplastic Cells.

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

REVISTA / JOURNAL: - Nutr Cancer. 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.812225](#)

AUTORES / AUTHORS: - Soares ND; Teodoro AJ; Oliveira FL; Santos CA; Takiya CM; Junior OS; Bianco M; Junior AP; Nasciutti LE; Ferreira LB; Gimba ER; Borojevic R

INSTITUCIÓN / INSTITUTION: - a Programa de Pesquisa em Ciencia de Alimentos, Instituto de Quimica, Universidade Federal do Rio de Janeiro , Rio de Janeiro , Brazil.

RESUMEN / SUMMARY: - Prostate cancer is the most common malignancy in men and the second leading cause of cancer-related mortality in men of the Western world.

Lycopene has received attention because of its expected potential to prevent cancer. In the present study, we evaluated the influence of lycopene on cell viability, cell cycle, and apoptosis of human prostate cancer cells and benign prostate hyperplastic cells. Using MTT assay, we observed a decrease of cell viability in all cancer cell lines after treatment with lycopene, which decreased the percentage of cells in G0/G1 phase and increased in S and G2/M phases after 96 h of treatment in metastatic prostate cancer cell lineages. Flow cytometry analysis of cell cycle revealed lycopene promoted cell cycle arrest in G0/G1 phase after 48 and 96 h of treatment in a primary cancer cell line. Using real time PCR assay, lycopene also induced apoptosis in prostate cancer cells with altered gene expression of Bax and Bcl-2. No effect was observed in benign prostate hyperplasia cells. These results suggest an effect of lycopene on activity of human prostate cancer cells.

[370]

TÍTULO / TITLE: - The Integrin Inhibitor Cilengitide Affects Meningioma Cell Motility and Invasion.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5402-5412. Epub 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-0299](#)

AUTORES / AUTHORS: - Wilisch-Neumann A; Kliese N; Pachow D; Schneider T; Warnke JP; Braunsdorf WE; Bohmer FD; Hass P; Pasemann D; Helbing C; Kirches E; Mawrin C

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Departments of Neuropathology, Neurosurgery and Radiotherapy, Otto vonGuericke University; Neurosurgery, City Hospital; Special Lab for Non-Invasive Brain Imaging, Leibniz Institute for Neurobiology, Magdeburg; Neurosurgery, Paracelsus Hospital, Zwickau; and Institute of Molecular Cell Biology, Center for Molecular Biomedicine, Jena University Hospital, Jena, Germany.

RESUMEN / SUMMARY: - PURPOSE: Meningiomas are frequent intracranial or spinal neoplasms, which recur frequently and can show aggressive clinical behaviour. We

elucidated the impact of the integrin inhibitor cilengitide on migration, proliferation, and radiosensitization of meningioma cells. EXPERIMENTAL DESIGN: We analyzed integrin expression in tissue microarrays of human meningiomas and the antimeningioma properties of cilengitide in cell cultures, subcutaneous and intracranial nude mouse models by measuring tumor volumes and survival times. RESULTS: $\alpha 5 \beta 1$ was the predominantly expressed integrin heterodimer in meningiomas, whereas $\alpha 3 \beta 1$ was mainly detected in tumor blood vessels. Application of up to 100 $\mu\text{g}/\text{mL}$ cilengitide resulted in only mildly reduced proliferation/survival of meningioma cell lines. Effects on cell survival could be enhanced by irradiation. One $\mu\text{g}/\text{mL}$ cilengitide was sufficient to significantly inhibit meningioma cell migration and invasion in vitro. A daily dosage of 75 mg/kg did neither affect tumor volumes nor overall survival ($P = 0.813$, log-rank test), but suppressed brain invasion in a significant fraction of treated animals. A combination of 75 mg/kg cilengitide daily and irradiation (2 x 5 Gy) led to a 67% reduction of MRI-estimated tumor volumes in the intracranial model ($P < 0.01$), whereas the corresponding reduction reached by irradiation alone was only 55% ($P < 0.05$). CONCLUSIONS: These data show that a monotherapy with cilengitide is not likely to achieve major responses in rapidly growing malignant meningiomas, although brain invasion may be reduced because of the strong antimigratory properties of the drug. The combination with radiotherapy warrants further attention. Clin Cancer Res; 19(19); 5402-12. ©2013 AACR.

[371]

TÍTULO / TITLE: - Salinomycin induces apoptosis in cisplatin-resistant colorectal cancer cells by accumulation of reactive oxygen species.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Oct 24;222(2):139-45. doi: 10.1016/j.toxlet.2013.07.022. Epub 2013 Aug 2.

●● Enlace al texto completo (gratis o de pago) [1016/j.toxlet.2013.07.022](#)

AUTORES / AUTHORS: - Zhou J; Li P; Xue X; He S; Kuang Y; Zhao H; Chen S; Zhi Q; Guo X

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, 215006, China.

RESUMEN / SUMMARY: - Postoperative chemotherapy for Colorectal cancer (CRC) patients is not all effective and the main reason might lie in cancer stem cells (CSCs). Emerging studies showed that CSCs overexpress some drug-resistance related proteins, which efficiently transport the chemotherapeutics out of cancer cells. Salinomycin, which considered as a novel and an effective anticancer drug, is found to have the ability to kill both CSCs and therapy-resistant cancer cells. To explore the potential mechanisms that salinomycin could specifically target on therapy-resistant cancer cells in colorectal cancers, we firstly obtained cisplatin-resistant (Cisp-resistant) SW620 cells by repeated exposure to 5 $\mu\text{mol}/\text{l}$ of cisplatin from an original colorectal

cancer cell line. These Cisp-resistant SW620 cells, which maintained a relative quiescent state (G0/G1 arrest) and displayed stem-like signatures (up-regulations of Sox2, Oct4, Nanog, Klf4, Hes1, CD24, CD26, CD44, CD133, CD166, Lgr5, ALDH1A1 and ALDH1A3 mRNA expressions) ($p < 0.05$), were sensitive to salinomycin ($p < 0.05$). Salinomycin did not show the influence on the cell cycle of Cisp-resistant SW620 cells ($p > 0.05$), but could induce cell death process ($p < 0.05$), with increased levels of LDH release and MDA contents as well as down-regulations of SOD and GSH-PX activities ($p < 0.05$). Our data also showed that the pro-apoptotic genes (Caspase-3, Caspase-8, Caspase-9 and Bax) were up-regulated and the anti-apoptotic gene Bcl-2 were down-regulated in Cisp-resistant SW620 cells ($p < 0.05$). Accumulated reactive oxygen species and dysregulation of some apoptosis-related genes might ultimately lead to apoptosis in Cisp-resistant SW620 cells. These findings will provide new clues for novel and selective chemotherapy on cisplatin-resistant colorectal cancer cells.

[372]

TÍTULO / TITLE: - Macrophages mediate gemcitabine resistance of pancreatic adenocarcinoma by upregulating cytidine deaminase.

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

REVISTA / JOURNAL: - Oncogene. 2013 Sep 2. doi: 10.1038/onc.2013.357.

●● [Enlace al texto completo \(gratis o de pago\) 1038/onc.2013.357](#)

AUTORES / AUTHORS: - Weizman N; Krelin Y; Shabtay-Orbach A; Amit M; Binenbaum Y; Wong RJ; Gil Z

INSTITUCIÓN / INSTITUTION: - The Laboratory for Applied Cancer Research, Department of Otolaryngology Head and Neck Surgery, Rambam Medical Center, Haifa, Israel.

RESUMEN / SUMMARY: - Resistance to pharmacologic agents used in chemotherapy is common in most human carcinomas, including pancreatic ductal adenocarcinoma (PDA), which is resistant to almost all drugs, including gemcitabine, a nucleoside analog used as a first-line treatment. Poor survival rates of PDA patients have, therefore, not changed much over 4 decades. Recent data indicated that tumor-associated macrophages (TAMs), which are abundant in the microenvironment of several tumors, including PDA, secrete pro-tumorigenic factors that contribute to cancer progression and dissemination. In this study, we show for the first time that TAMs can also induce chemoresistance of PDA by reducing gemcitabine-induced apoptosis. Macrophages co-cultured with cancer cells or TAM-conditioned medium significantly reduced apoptosis and activation of the caspase-3 pathway during gemcitabine treatment. In vivo PDA models of mice, which have reduced macrophage recruitment and activation, demonstrated improved response to gemcitabine compared with controls. Similarly, inhibition of monocytes/macrophages trafficking by a CSF1-receptor antagonist GW2580 augmented the effect of gemcitabine in a transgenic mouse PDA model that was resistant to gemcitabine alone. Analysis of

multiple proteins involved in gemcitabine delivery and metabolism revealed that TAMs induced upregulation of cytidine deaminase (CDA), the enzyme that metabolizes the drug following its transport into the cell. Decreasing CDA expression by PDA cells blocked the protective effect of TAMs against gemcitabine. These results provide the first evidence of a paracrine effect of TAMs, which mediates acquired resistance of cancer cells to chemotherapy. Modulation of macrophage trafficking or inhibition of CDA may offer a new strategy for augmenting the response of PDA to chemotherapy. *Oncogene* advance online publication, 2 September 2013; doi:10.1038/onc.2013.357.

[373]

TÍTULO / TITLE: - Polyphenols isolated from *Allium cepa* L. induces apoptosis by suppressing IAP-1 through inhibiting PI3K/Akt signaling pathways in human leukemic cells.

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

REVISTA / JOURNAL: - *Food Chem Toxicol.* 2013 Sep 7;62C:382-389. doi: 10.1016/j.fct.2013.08.085.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.08.085](#)

AUTORES / AUTHORS: - Han MH; Lee WS; Jung JH; Jeong JH; Park C; Kim HJ; Kim G; Jung JM; Kwon TK; Kim GY; Ryu CH; Shin SC; Hong SC; Choi YH

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Dongeui University College of Oriental Medicine and 3Anti-Aging Research Center & Blue-Bio Industry RIC, Dongeui University, Busan 614-052, South Korea.

RESUMEN / SUMMARY: - *Allium cepa* Linn is commonly used as supplementary folk remedy for cancer therapy. Evidence suggests that *Allium* extracts have anti-cancer properties. However, the mechanisms of the anti-cancer activity of *A. cepa* Linn are not fully elucidated in human cancer cells. In this study, we investigated anti-cancer effects of polyphenols extracted from lyophilized *A. cepa* Linn (PEAL) in human leukemia cells and their mechanisms. PEAL inhibited cancer cell growth by inducing caspase-dependent apoptosis. The apoptosis was suppressed by caspase 8 and 9 inhibitors. PEAL also up-regulated TNF-related apoptosis-inducing ligand (TRAIL) receptor DR5 and down-regulated survivin and cellular inhibitor of apoptosis 1 (cIAP-1). We confirmed these findings in other leukemic cells (THP-1, K562 cells). In addition, PEAL suppressed Akt activity and the PEAL-induced apoptosis was significantly attenuated in Akt-overexpressing U937 cells. In conclusion, our data suggested that PEAL induced caspase-dependent apoptosis in several human leukemic cells including U937 cells. The apoptosis was triggered through extrinsic pathway by up-regulating DR5 modulating as well as through intrinsic pathway by modulating IAP family members. In addition, PEAL induces caspase-dependent apoptosis at least in part

through the inhibition of phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. This study provides evidence that PEAL might be useful for the treatment of leukemia.

[374]

TÍTULO / TITLE: - Rotenone-induced oxidative stress and apoptosis in human liver HepG2 cells.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1781-9](#)

AUTORES / AUTHORS: - Siddiqui MA; Ahmad J; Farshori NN; Saquib Q; Jahan S; Kashyap MP; Ahamed M; Musarrat J; Al-Khedhairi AA

INSTITUCIÓN / INSTITUTION: - Department of Zoology, College of Science, King Saud University, P.O. Box 2455, Riyadh, 11451, Saudi Arabia, maqsoodahmads@gmail.com.

RESUMEN / SUMMARY: - Rotenone, a commonly used pesticide, is well documented to induce selective degeneration in dopaminergic neurons and motor dysfunction. Such rotenone-induced neurodegeneration has been primarily suggested through mitochondria-mediated apoptosis and reactive oxygen species (ROS) generation. But the status of rotenone induced changes in liver, the major metabolic site is poorly investigated. Thus, the present investigation was aimed to study the oxidative stress-induced cytotoxicity and apoptotic cell death in human liver cells-HepG2 receiving experimental exposure of rotenone (12.5-250 μ M) for 24 h. Rotenone depicted a dose-dependent cytotoxic response in HepG2 cells. These cytotoxic responses were in concurrence with the markers associated with oxidative stress such as an increase in ROS generation and lipid peroxidation as well as a decrease in the glutathione, catalase, and superoxide dismutase levels. The decrease in mitochondrial membrane potential also confirms the impaired mitochondrial activity. The events of cytotoxicity and oxidative stress were found to be associated with up-regulation in the expressions (mRNA and protein) of pro-apoptotic markers viz., p53, Bax, and caspase-3, and down-regulation of anti-apoptotic marker Bcl-2. The data obtain in this study indicate that rotenone-induced cytotoxicity in HepG2 cells via ROS-induced oxidative stress and mitochondria-mediated apoptosis involving p53, Bax/Bcl-2, and caspase-3.

[375]

TÍTULO / TITLE: - Cyclin-dependent kinase 11 (CDK11) is crucial in the growth of liposarcoma cells.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Sep 2. pii: S0304-3835(13)00625-3. doi: 10.1016/j.canlet.2013.08.040.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.08.040](#)

AUTORES / AUTHORS: - Jia B; Choy E; Cote G; Harmon D; Ye S; Kan Q; Mankin H; Hornicek F; Duan Z

INSTITUCIÓN / INSTITUTION: - Sarcoma Biology Laboratory, Center for Sarcoma and Connective Tissue Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; Department of Pharmacology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China.

RESUMEN / SUMMARY: - Liposarcoma is the second most common soft tissue sarcoma in adults, but treatment options have been quite limited thus far. In this study, we investigated the functional and therapeutic relevance of cyclin-dependent kinase 11 (CDK11) as a putative target in liposarcoma. CDK11 knockdown by synthetic siRNA or lentiviral shRNA decreased cell proliferation, and induced apoptosis in liposarcoma cells. Moreover, CDK11 knockdown enhances the cytotoxic effect of doxorubicin to inhibit cell growth in liposarcoma cells. These findings suggest that CDK11 is critical for the growth and proliferation of liposarcoma cells. CDK11 may be a promising therapeutic target for the treatment of liposarcoma patients.

[376]

TÍTULO / TITLE: - Association of Exon 19 and 21 EGFR Mutation Patterns with Treatment Outcome after First-Line Tyrosine Kinase Inhibitor in Metastatic Non-Small-Cell Lung Cancer.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Sep;8(9):1148-55. doi: 10.1097/JTO.0b013e31829f684a.

●● [Enlace al texto completo \(gratis o de pago\) 1097/JTO.0b013e31829f684a](#)

AUTORES / AUTHORS: - Lee VH; Tin VP; Choy TS; Lam KO; Choi CW; Chung LP; Tsang JW; Ho PP; Leung DK; Ma ES; Liu J; Shek TW; Kwong DL; Leung TW; Wong MP

INSTITUCIÓN / INSTITUTION: - Departments of *Clinical Oncology and daggerPathology, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, People's Republic of China; double daggerDepartment of Community Medicine, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, People's Republic of China; and section signDepartment of Pathology, Hong Kong Sanatorium and Hospital, Hong Kong, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: This study investigated whether there were differential survival outcomes to first-line tyrosine kinase inhibitors (TKI) in patients with metastatic non-small-cell lung cancer harboring different subtypes of exon 19 and exon 21 mutations on epidermal growth factor receptor (EGFR). METHODS: Of 452 patients with stage IIIB and IV non-small-cell lung cancer, 192 patients (42.5%) harbored EGFR mutation and 170 (37.5%) received TKI as first-line treatment. EGFR mutation analysis was performed by direct sequencing. Survival and response outcome

were compared among different subtypes of exon 19 and exon 21 EGFR mutations in these 170 patients. RESULTS: Patients harboring exon 19 18-nucleotide deletion (delL747_P753insS) had the shortest median progression-free survival (PFS) (6.5 months), followed by those with 15-nucleotide deletion (delE746_A750) (12.4 months) and mixed insertion/substitution mutations (22.3 months; $p = 0.012$). However, patients who had exon 19 deletions starting on codon E746 had better median PFS (14.2 months) than those starting on L747 (6.5 months; hazard ratio, 0.445; 95% confidence interval [0.219-0.903]; $p = 0.021$). Besides, exon 21 L858R derived a longer median PFS than L861R/L861Q (11.4 months versus 2.1 months, respectively; hazard ratio, 0.298; 95% confidence interval [0.090-0.980]; $p = 0.034$). CONCLUSIONS: Different subtypes of EGFR exon 19 and 21 mutations exhibited differential survival to first-line TKI therapy. Detailed sequence evaluation of exon 19 deletions may provide important prognostic information on survival outcome after TKI.

[377]

TÍTULO / TITLE: - Phosphorylated s6 kinase-1: a breast cancer marker predicting resistance to neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):4073-9.

AUTORES / AUTHORS: - Kim EK; Kim JH; Kim HA; Seol H; Seong MK; Lee JY; Byeon J; Sohn YJ; Koh JS; Park IC; Noh WC

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, 215-4 Gongneung-dong, Nowon-gu 139-706, Seoul, Korea. nohwoo@kcch.re.kr.

RESUMEN / SUMMARY: - BACKGROUND: Pre-clinical data support a link between the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway and chemoresponsiveness. We evaluated whether the expression of phosphorylated AKT (p-AKT) or phosphorylated S6 kinase-1 (p-S6K1), a key effector of the mTOR pathway, could be a predictive marker for chemoresponsiveness in breast cancer. PATIENTS AND METHODS: A total of 209 patients with locally advanced breast cancer who received neoadjuvant chemotherapy between April 2005 and July 2012 were analyzed. Patients without a minimum of 10% tumor reduction, after neoadjuvant chemotherapy, were classified as non-responders. RESULTS: Overall, 184 (88%) patients were classified as responders and 25 (12%) as non-responders. The positive expression rate for p-AKT and p-S6K1 was 31.6% and 45%, respectively. There was no difference in the pre-chemotherapy clinical stage according to p-S6K1 or p-AKT expression status. p-AKT expression was slightly higher in non-responders compared to responders (48% vs. 30.9%; $p=0.088$). However, p-S6K1 expression was significantly higher in non-responders than responders (68% vs. 41.8%; $p=0.014$). Following multivariate analysis, p-S6K1 positivity remained an independent

predictor of non-responder status (hazard ratio=3.81; 95% confidence interval=1.28-11.31; p=0.016). CONCLUSION: The expression of p-S6K1 may be a predictive marker of resistance to neoadjuvant chemotherapy in patients with breast cancer.

[378]

TÍTULO / TITLE: - Heat shock protein 70 (HSP70) expression is associated with poor prognosis in intestinal type gastric cancer.

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

REVISTA / JOURNAL: - Virchows Arch. 2013 Oct;463(4):489-495. Epub 2013 Aug 4.

●● Enlace al texto completo (gratis o de pago) [1007/s00428-013-1461-x](#)

AUTORES / AUTHORS: - Lee HW; Lee EH; Kim SH; Roh MS; Jung SB; Choi YC

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Samsung Changwon Hospital, School of Medicine, Sungkyunkwan University, Changwon, South Korea.

RESUMEN / SUMMARY: - Heat shock protein 70 (HSP70) is a molecular chaperone which plays an important role in cellular protection against various stressful stimuli and in the regulation of cellular growth and apoptosis. This study was conducted in gastric carcinoma (GC) to assess correlations of HSP70 expression with clinicopathological parameters and overall survival (OS). Tissue microarray blocks were constructed from 172 GCs and immunohistochemically stained for HSP70. Low HSP70 expression was found in 122 GCs (71 %), whereas 50 (29 %) had high expression. HSP70 expression was higher in tumours in the cardia (p = 0.008), with non-signet ring cell histology (p < 0.001), of intestinal type (p = 0.045) and of higher pathological T stage (p = 0.026). When considering the cohort as a whole, HSP70 expression did not correlate with OS (p = 0.092). In intestinal type carcinomas, however, high HSP70 expression significantly correlated with worse OS (p = 0.034). These results suggest that HSP70 expression might be an unfavourable prognostic factor in patients with GC, especially of intestinal type.

[379]

TÍTULO / TITLE: - High expression of spindle assembly checkpoint proteins CDC20 and MAD2 is associated with poor prognosis in urothelial bladder cancer.

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

REVISTA / JOURNAL: - Virchows Arch. 2013 Aug 31.

●● Enlace al texto completo (gratis o de pago) [1007/s00428-013-1473-6](#)

AUTORES / AUTHORS: - Choi JW; Kim Y; Lee JH; Kim YS

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Korea University Ansan Hospital, 516, Gojan-1 Dong, Danwon-Gu, Ansan-Si, Gyeonggi-Do, 425-707, Republic of Korea.

RESUMEN / SUMMARY: - Aneuploidy is a result of the abnormal expression of spindle assembly checkpoint (SAC) proteins and resulting abnormal spindle function during

mitosis. High expression of cell division cycle 20 homolog (CDC20) and mitotic arrest defective protein 2 (MAD2), key components of the SAC, has been reported in various carcinomas. However, the clinicopathological significance of CDC20 and MAD2 expressions in urothelial carcinoma of the human bladder (UCB) is unknown. We therefore studied the expression of CDC20 and MAD2 in UCB specimens by immunohistochemistry. High expression of CDC20 and MAD2 was observed in 59.0 % (200/339) and 51.0 % (173/339) of UCB cases, respectively. Most high-grade tumor cells exhibited diffuse nuclear and/or cytoplasmic staining for CDC20 and MAD2, whereas most low-grade tumor cells and normal urothelial cells were not stained. CDC20 overexpression was associated with advanced age ($p = 0.010$), high grade ($p < 0.001$), advanced stage ($p < 0.001$), non-papillary growth pattern ($p < 0.001$), and distant metastasis ($p = 0.042$). Similarly, high MAD2 expression correlated with high grade ($p < 0.001$), advanced stage ($p < 0.001$), and non-papillary growth pattern ($p < 0.001$). In univariate survival analyses, high CDC20 expression correlated with shorter recurrence-free survival (RFS) ($p = 0.032$) and poorer overall survival (OS) ($p = 0.007$) in patients with UCB, whereas high MAD2 expression was associated with poorer OS ($p = 0.008$). In multivariate analyses, high CDC20 expression correlated with shorter RFS of patients with Ta stage UCB (hazard ratio, 1.91; $p = 0.01$). In conclusion, increased expression of CDC20 and MAD2 is related to poor prognosis of UCB.

[380]

TÍTULO / TITLE: - High levels of secreted frizzled-related protein 1 correlate with poor prognosis and promote tumorigenesis in gastric cancer.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 5. pii: S0959-8049(13)00561-3. doi: 10.1016/j.ejca.2013.07.011.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejca.2013.07.011

AUTORES / AUTHORS: - Qu Y; Ray PS; Li J; Cai Q; Bagaria SP; Moran C; Sim MS; Zhang J; Turner RR; Zhu Z; Cui X; Liu B

INSTITUCIÓN / INSTITUTION: - Shanghai Key Laboratory of Gastric Neoplasms, Department of Surgery, Shanghai Institute of Digestive Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China.

RESUMEN / SUMMARY: - BACKGROUND: Secreted frizzled-related protein 1 (sFRP1), Wnt signalling regulator, can positively or negatively regulate tumorigenesis and progression. We sought to determine the clinical relevance and the role of sFRP1 in gastric cancer development and progression. METHODS: We investigated the sFRP1 protein expression levels and its clinicopathological correlations using 85 cases of human gastric samples with survival information (JWCI cohort). mRNA levels of sFRP1 and coexpressed genes were analysed using 131-sample cDNA microarray data (Ruijin cohort). The effects of sFRP1 alteration were investigated using cell proliferation,

colony formation, migration, and invasion and xenograft models. RESULTS: We show that sFRP1 is overexpressed in some human cancers and is significantly associated with lymph node metastasis and decreased overall survival in gastric cancer patients. Using gastric cancer cell models, we demonstrate that sFRP1 overexpression is correlated with the activation of TGFbeta (transforming growth factor-beta) signalling pathway and thereby induces cell proliferation, epithelial-mesenchymal transition (EMT), and invasion. Conversely, sFRP1 knockdown shows the opposite effects. Furthermore, sFRP1 overexpression promotes tumorigenesis and metastasis in a xenograft model. CONCLUSION: Our studies demonstrate that sFRP1 is a biomarker for aggressive subgroups of human gastric cancer and a prognostic biomarker for patients with poor survival. Our data provide insight into a crosstalk between Wnt and TGFbeta pathways which underlies gastric cancer development and progression.

[381]

TÍTULO / TITLE: - Functional proteomics characterization of residual triple-negative breast cancer after standard neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Oct;24(10):2522-6. doi: 10.1093/annonc/mdt248. Epub 2013 Aug 7.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt248](#)

AUTORES / AUTHORS: - Sohn J; Do KA; Liu S; Chen H; Mills GB; Hortobagyi GN; Meric-Bernstam F; Gonzalez-Angulo AM

INSTITUCIÓN / INSTITUTION: - Departments of Breast Medical Oncology.

RESUMEN / SUMMARY: - BACKGROUND: In this study, we used functional proteomics to determine the molecular characteristics of residual triple receptor-negative breast cancer (TNBC) patients after neoadjuvant systemic chemotherapy (NCT) and their relationship with patient outcomes in order to identify potential targets for therapy. PATIENTS AND METHODS: Protein was extracted from 54 residual TNBCs, and 76 proteins related to breast cancer signaling were measured by reverse phase protein arrays (RPPAs). Univariable and multivariable Cox proportional hazard models were fitted for each protein. Survival outcomes were estimated by the Kaplan-Meier product limit method. Training and cross validation were carried out. The coefficients estimated from the multivariable Cox model were used to calculate a risk score (RS) for each sample. RESULTS: Multivariable analysis using the top 25 proteins from univariable analysis at a false discovery rate (FDR) of 0.3 showed that AKT, IGFBP2, LKB1, S6 and Stathmin were predictors of recurrence-free survival (RFS). The cross-validation model was reproducible. The RS model calculated based on the multivariable analysis was $-1.1086 \times \text{AKT} + 0.2501 \times \text{IGFBP2} - 0.6745 \times \text{LKB1} + 1.0692 \times \text{S6} + 1.4086 \times \text{stathmin}$ with a corresponding area under the curve, AUC = 0.856. The RS was an independent predictor of RFS (HR = 3.28, 95%CI = 2.07-5.20, P < 0.001).

CONCLUSIONS: We found a five-protein model that independently predicted RFS risk in patients with residual TNBC disease. The PI3 K pathway may represent potential therapeutic targets in this resistant disease.

[382]

TÍTULO / TITLE: - The mTOR kinase inhibitors, CC214-1 and CC214-2, preferentially block the growth of EGFRvIII-activated glioblastomas.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 12.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-13-0527](#)

AUTORES / AUTHORS: - Gini B; Zanca C; Guo D; Matsutani T; Masui K; Ikegami S; Yang H; Nathanson D; Villa G; Shackelford D; Zhu S; Tanaka K; Babic I; Akhavan D; Lin K; Assuncao A; Gu Y; Bonetti B; Mortensen DS; Xu S; Raymon H; Cavenee WK; Furnari FB; James CD; Kroemer G; Heath JR; Hege K; Chopra R; Cloughesy TF; Mischel PS

INSTITUCIÓN / INSTITUTION: - Ludwig Institute for Cancer Research, UCSD.

RESUMEN / SUMMARY: - PURPOSE: mTOR pathway hyperactivation occurs in nearly 90% of glioblastomas, but the allosteric mTOR inhibitor rapamycin has failed in the clinic. Here we examine the efficacy of the newly discovered ATP-competitive mTOR kinase inhibitors CC214-1 and CC214-2 in glioblastoma, identifying molecular determinants of response and mechanisms of resistance, and develop a pharmacological strategy to overcome it. EXPERIMENTAL DESIGN: We performed in vitro and in vivo studies in glioblastoma cell lines and an intracranial model to: determine the potential efficacy of the recently reported mTOR kinase inhibitors CC214-1 (in vitro use) and CC214-2 (in vivo use) at inhibiting rapamycin resistant signaling and blocking GBM growth and a novel single cell technology, DNA Encoded Antibody Libraries, was used to identify mechanisms of resistance. RESULTS: Here we demonstrate that CC214-1 and CC214-2 suppress rapamycin-resistant mTORC1 signaling; block mTORC2 signaling and significantly inhibit the growth of glioblastomas in vitro and in vivo. EGFRvIII expression and PTEN loss enhance sensitivity to CC214 compounds, consistent with enhanced efficacy in strongly mTOR-activated tumors. Importantly, CC214 compounds potently induce autophagy, preventing tumor cell death. Genetic or pharmacologic inhibition of autophagy greatly sensitizes GBM cells and orthotopic xenografts to CC214-1 and CC214-2 induced cell death. CONCLUSIONS: These results identify CC214-1 and CC214-2 as potentially efficacious mTOR kinase inhibitors in GBM and suggest a strategy for identifying patients most likely to benefit from mTOR inhibition. This study also demonstrates a central role for autophagy in preventing mTOR-kinase inhibitor-mediated tumor cell death, and suggests a pharmacological strategy for overcoming it.

[383]

TÍTULO / TITLE: - JWA inhibits melanoma angiogenesis by suppressing ILK signaling and is an independent prognostic biomarker for melanoma.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt318](#)

AUTORES / AUTHORS: - Lu J; Tang Y; Farshidpour M; Cheng Y; Zhang G; Jafarnejad SM; Yip A; Martinka M; Dong Z; Zhou J; Xu J; Li G

INSTITUCIÓN / INSTITUTION: - Department of Dermatology and Skin Science, Research Pavilion, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia, Canada.

RESUMEN / SUMMARY: - Melanoma is the deadliest cutaneous malignancy because of its high incidence of metastasis. Melanoma growth and metastasis relies on sustained angiogenesis; therefore, inhibiting angiogenesis is a promising approach to treat metastatic melanoma. JWA is a novel microtubule-associated protein and our previous work revealed that JWA inhibited melanoma cell invasion and metastasis. However, the role of JWA in melanoma angiogenesis and the prognostic value are still unknown. Here, we report that JWA in melanoma cells significantly inhibited the tube formation of endothelial cells. In addition, JWA regulated ILK through integrin α v β 3 and such regulation was achieved through the transcription factor Sp1. Notably, both in vitro and in vivo angiogenesis assays revealed that JWA dramatically suppressed melanoma angiogenesis by inhibiting ILK signaling. Furthermore, we examined the expression of JWA protein in a large set of melanocytic lesions (n=505) at different stages by tissue microarray and found an inverse correlation between JWA expression and melanoma progression (P=5x10⁻⁶). Importantly, reduced JWA expression was correlated with a poorer overall, and disease-specific, 5-year survival of patients (P=0.001 and 0.007, respectively). Multivariate Cox regression analyses indicated that JWA was an independent prognostic marker for melanoma patients. Moreover, we found a significant negative correlation between JWA and ILK in melanoma biopsies, and their concomitant expression was closely correlated with melanoma patient survival (P=0.004), further indicating the regulation of ILK expression by JWA is critical in melanoma. Taken together, our data highlight the function of JWA in melanoma angiogenesis and reveal the clinical prognostic value of JWA.

[384]

TÍTULO / TITLE: - A ruthenium(II) beta-carboline complex induced p53-mediated apoptosis in cancer cells.

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

REVISTA / JOURNAL: - Biochimie. 2013 Nov;95(11):2050-2059. doi: 10.1016/j.biochi.2013.07.016. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1016/j.biochi.2013.07.016](#)

AUTORES / AUTHORS: - Chen Y; Qin MY; Wang L; Chao H; Ji LN; Xu AL

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biocontrol, Department of Biochemistry, College of Life Sciences, Sun Yat-sen University, Guangzhou 510006, PR China.

RESUMEN / SUMMARY: - A ruthenium(II) beta-carboline complex [Ru(tpy)(Nh)3]2+ (tpy = 2,2':6',2''-terpyridine, Nh = Norharman, Ru1) has been synthesized and characterized. This complex induced apoptosis against various cancer cell lines and had high selectivity between tumor cells and normal cells. In vivo examination indicated Ru1 decreased mouse MCF-7 and HepG2 tumor growth. Signaling pathways analysis demonstrated that this complex induced apoptosis via the mitochondrial pathway, as evidenced by the loss of mitochondrial membrane potential (MMP, DeltaPsim) and the release of cytochrome c. The resulting accumulation of p53 proteins from phosphorylation at Ser-15 and Ser-392 correlated with an increase in p21 and caspase activation. Taken together, these findings suggest that Ru1 exhibits high and selective cytotoxicity induced p53-mediated apoptosis and may contribute to the future development of improved chemotherapeutics against human cancers.

[385]

TÍTULO / TITLE: - ONTD induces apoptosis of human hepatoma Bel-7402 cells via a MAPK-dependent mitochondrial pathway and the depletion of intracellular glutathione.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Sep 11;45(11):2632-2642. doi: 10.1016/j.biocel.2013.08.021.

●● Enlace al texto completo (gratis o de pago) [1016/j.biocel.2013.08.021](#)

AUTORES / AUTHORS: - Tan J; Lai Z; Liu L; Long W; Chen T; Zha J; Wang L; Chen M; Ji H; Lai Y

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China; Department of Pharmacology, China Pharmaceutical University, Nanjing 210009, PR China.

RESUMEN / SUMMARY: - 3-Oxo-29-noroleana-1,9(11),12-trien-2,20-dicarbonitrile (ONTD) is a novel synthetic derivative of glycyrrhetic acid (GA), which has the ability to inhibit the proliferation of human hepatocellular carcinoma (HCC) cells. However, the mechanisms by which ONTD exerts its inhibitory effects remain elusive. The present study was conducted to investigate the cytotoxicity of ONTD in Bel-7402 cells and its molecular mechanisms. We found that ONTD depleted intracellular GSH, increased the level of ROS, and consequently induced mitochondrial permeability transition (MPT) leading to the release of apoptosis-inducing factor (AIF) and cytochrome c (Cyt c) to the cytosol. Mitochondrial alteration and subsequent apoptotic cell death in ONTD-treated Bel-7402 cells could be blocked by addition of exogenous antioxidants N-

acetylcystein (NAC), GSH and the MTP inhibitor cyclosporin A (CsA). In addition, ONTD activated the phosphorylation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases (MAPK) but not extracellular signal-regulated protein kinases (ERK ½). When the cells were exposed to SP600125 (a JNK inhibitor) and SB203580 (a p38 inhibitor), the deregulation of the expression of apoptotic proteins was attenuated. Furthermore, 40mg/kg ONTD significantly reduced tumor weight (-70.62%, p<0.01) in the H22 tumor-bearing mouse model in vivo. Taken together, these findings provide the first experimental evidence supporting that ONTD could induce apoptosis of Bel-7402 cells via MAPK-mediated mitochondrial pathway and ONTD has the potential to be developed as a therapeutic agent for the treatment of HCC.

[386]

TÍTULO / TITLE: - Antitumour activity on extrinsic apoptotic targets of the triterpenoid maslinic acid in p53-deficient Caco-2 adenocarcinoma cells.

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

REVISTA / JOURNAL: - Biochimie. 2013 Nov;95(11):2157-2167. doi: 10.1016/j.biochi.2013.08.017. Epub 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1016/j.biochi.2013.08.017](#)

AUTORES / AUTHORS: - Reyes-Zurita FJ; Rufino-Palomares EE; Medina PP; Leticia Garcia-Salguero E; Peragon J; Cascante M; Lupianez JA

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology I, University of Granada, 18071 Granada, España. Electronic address: ferjes@ugr.es.

RESUMEN / SUMMARY: - We report that a novel triterpenoid, (2^a,3b)-2,3-dihydroxyolean-12-en-28-oic acid (maslinic acid), isolated from olive pomace from *Olea europaea*, triggers primarily the extrinsic and later the intrinsic apoptotic pathways in Caco-2 human colon-cancer cells. Apoptosis induced by maslinic acid was confirmed by FACS analysis using annexin-V FICT staining. This induction of apoptosis was correlated with the early activation of caspase-8 and caspase-3, the activation of caspase-8 was also correlated with higher levels of Bid cleavage and decreased Bcl-2, but with no change in Bax expression. Maslinic acid also induced a sustained activation of c-Jun N-terminal kinase (JNK). Incubation with maslinic acid also resulted in the later activation of caspase-9, which, together with the lack of any Bax activation, suggests that the mitochondrial pathway is not required for apoptosis induced by maslinic acid in this cell line. In this study we found that the mechanism of apoptotic activation in p53-deficient Caco-2 cells differs significantly from that found in HT-29 cells. Natural agents able to activate both the extrinsic and intrinsic apoptotic pathways by avoiding the mitochondrial resistance mechanisms may be useful for treatment against colon cancer regardless of its aetiology.

[387]

TÍTULO / TITLE: - Large-scale prediction of human kinase-inhibitor interactions using protein sequences and molecular topological structures.

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

REVISTA / JOURNAL: - Anal Chim Acta. 2013 Aug 20;792:10-8. doi: 10.1016/j.aca.2013.07.003. Epub 2013 Jul 10.

●● Enlace al texto completo (gratis o de pago) [1016/j.aca.2013.07.003](#)

AUTORES / AUTHORS: - Cao DS; Zhou GH; Liu S; Zhang LX; Xu QS; He M; Liang YZ

INSTITUCIÓN / INSTITUTION: - School of Pharmaceutical Sciences, Central South University, Changsha 410013, PR China. oriental-cds@163.com

RESUMEN / SUMMARY: - The kinase family is one of the largest target families in the human genome. The family's key function in signal transduction for all organisms makes it a very attractive target class for the therapeutic interventions in many diseases states such as cancer, diabetes, inflammation and arthritis. A first step toward accelerating kinase drug discovery process is to fast identify whether a chemical and a kinase interact or not. Experimentally, these interactions can be identified by in vitro binding assay - an expensive and laborious procedure that is not applicable on a large scale. Therefore, there is an urgent need to develop statistically efficient approaches for identifying kinase-inhibitor interactions. For the first time, the quantitative binding affinities of kinase-inhibitor pairs are differentiated as a measurement to define if an inhibitor interacts with a kinase, and then a chemogenomics framework using an unbiased set of general integrated features (drug descriptors and protein descriptors) and random forest (RF) is employed to construct a predictive model which can accurately classify kinase-inhibitor pairs. Our results show that RF with integrated features gave prediction accuracy of 93.76%, sensitivity of 92.26%, and specificity of 95.27%, respectively. The results are superior to those by only considering two separated spaces (chemical space and protein space), demonstrating that these integrated features contribute cooperatively. Based on the constructed model, we provided a high confidence list of drug-target associations for subsequent experimental investigation guidance at a low false discovery rate.

[388]

TÍTULO / TITLE: - Chemical composition of total flavonoids from *Salvia chinensis* Benth and their pro-apoptotic effect on hepatocellular carcinoma cells: Potential roles of suppressing cellular NF-kappaB signaling.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Sep 12;62C:420-426. doi: 10.1016/j.fct.2013.09.008.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.09.008](#)

AUTORES / AUTHORS: - Su H; Hu Y; Hu Y; Yang T; Shu G

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, South-Central University for Nationalities, Wuhan, PR China.

RESUMEN / SUMMARY: - *Salvia chinensis* Benth (*S. chinensis*) is a medical plant that has been traditionally applied for centuries in the treatment of malignant diseases including hepatocellular carcinoma (HCC). However, the scientific basis underlying its anti-HCC activity has not been fully established. In this study, the chemical profiles of total flavonoids from *S. chinensis* (TFSC) were explored. Thirteen compounds which constituted the major components of TFSC were separated and identified. Flow cytometry analysis and caspase activity assays showed that TFSC dose-dependently induced HepG2 and Huh-7 HCC cell apoptosis. TFSC was also shown to substantially suppress NF-kappaB activity in HCC cells. Moreover, TFSC significantly repressed transplanted murine H22 ascitic hepatic cancer cell growth in vivo. Further studies revealed that TFSC induced HCC cell apoptosis and inhibited expression levels of NF-kappaB responsive genes in transplanted tumor tissues. In addition, the toxic impact of TFSC on tumor-bearing mice was undetectable. These results indicate that TFSC induces HCC cell apoptosis both in vitro and in vivo. The suppression of cellular NF-kappaB activity is implicated in the TFSC-mediated HCC cell apoptosis.

[389]

TÍTULO / TITLE: - Surface proteomic analysis of osteosarcoma identifies EPHA2 as receptor for targeted drug delivery.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 24. doi: 10.1038/bjc.2013.578.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.578](#)

AUTORES / AUTHORS: - Posthumadeboer J; Piersma SR; Pham TV; van Egmond PW; Knol JC; Cleton-Jansen AM; van Geer MA; van Beusechem VW; Kaspers GJ; van Royen BJ; Jimenez CR; Helder MN

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

RESUMEN / SUMMARY: - Background:Osteosarcoma (OS) is the most common bone tumour in children and adolescents. Despite aggressive therapy regimens, treatment outcomes are unsatisfactory. Targeted delivery of drugs can provide higher effective doses at the site of the tumour, ultimately improving the efficacy of existing therapy. Identification of suitable receptors for drug targeting is an essential step in the design of targeted therapy for OS.Methods:We conducted a comparative analysis of the surface proteome of human OS cells and osteoblasts using cell surface biotinylation combined with nano-liquid chromatography - tandem mass spectrometry-based proteomics to identify surface proteins specifically upregulated on OS cells. This approach generated an extensive data set from which we selected a candidate to study for its suitability as receptor for targeted treatment delivery to OS. First, surface

expression of the ephrin type-A receptor 2 (EPHA2) receptor was confirmed using FACS analysis. Ephrin type-A receptor 2 expression in human tumour tissue was tested using immunohistochemistry. Receptor targeting and internalisation studies were conducted to assess intracellular uptake of targeted modalities via EPHA2. Finally, tissue micro arrays containing cores of human OS tissue were stained using immunohistochemistry and EPHA2 staining was correlated to clinical outcome measures. Results: Using mass spectrometry, a total of 2841 proteins were identified of which 156 were surface proteins significantly upregulated on OS cells compared with human primary osteoblasts. Ephrin type-A receptor 2 was highly upregulated and the most abundant surface protein on OS cells. In addition, EPHA2 was expressed in a vast majority of human OS samples. Ephrin type-A receptor 2 effectively mediates internalisation of targeted adenoviral vectors into OS cells. Patients with EPHA2-positive tumours showed a trend toward inferior overall survival. Conclusion: The results presented here suggest that the EPHA2 receptor can be considered an attractive candidate receptor for targeted delivery of therapeutics to OS. British Journal of Cancer advance online publication, 24 September 2013; doi:10.1038/bjc.2013.578 www.bjcancer.com.

[390]

TÍTULO / TITLE: - Platycodin D, a triterpenoid saponin from *Platycodon grandiflorum*, induces G2/M arrest and apoptosis in human hepatoma HepG2 cells by modulating the PI3K/Akt pathway.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1169-1](#)

AUTORES / AUTHORS: - Qin H; Du X; Zhang Y; Wang R

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Tangdu Hospital, The Fourth Military Medicine University, Xi'an, Shaanxi, 710038, China.

RESUMEN / SUMMARY: - Platycodin D (PD) is one of triterpenoid saponins isolated from the roots of *Platycodon grandiflorum*. In the present study, we aimed at examining the antitumor activity of PD against human hepatoma HepG2 cancer cells and investigated the underlying molecular mechanisms of PD-induced apoptosis in HepG2 cells. PD significantly inhibited the proliferation of HepG2 cells in a concentration- and time-dependent manner as assessed by MTT assay. Besides, flow cytometry revealed that PD treatment obviously induced G2/M arrest and apoptosis in HepG2 cells. Moreover, Western blot analysis demonstrated that PD induced downregulation of protein expression of PI3K, P-Akt, and Bcl-2, whereas cleaved products of caspase-3 and -9 and PARP were upregulated by PD treatment. Furthermore, the protein level of P-p38, p-38, and Bax in PD-treated HepG2 cells was kept unchanged. In addition, the inhibitors of z-DEVD-fmk (a specific caspase-3 inhibitor) and z-LEHD-fmk (a specific caspase-9 inhibitor), but not z-IETD-fmk (a specific caspase-8 inhibitor), could significantly block

PD-triggered apoptosis, whereas LY294002 (Akt inhibitor) could significantly enhance PD-induced apoptosis in HepG2 cells. Thus, the increasing ratio of Bax to Bcl-2, activation of caspase-3 and -9 and PARP, and inactivation of the PI3K/Akt signaling pathway significantly enhanced PD-induced apoptosis in HepG2 cells. Our results suggest that PD induced cell cycle G2/M arrest and apoptosis in HepG2 cells by decreasing PI3K/Akt pathway. Therefore, we propose that PD has potential as a liver cancer chemotherapeutic agent.

[391]

TÍTULO / TITLE: - Curcumin induces osteosarcoma MG63 cells apoptosis via ROS/Cyto-C/Caspase-3 pathway.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1102-7](#)

AUTORES / AUTHORS: - Chang Z; Xing J; Yu X

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, General Hospital of Jinan Military Commanding Region, Jinan, 250031, Shandong, People's Republic of China.

RESUMEN / SUMMARY: - The antitumor effects of curcumin have attracted widespread attention worldwide. One of its major functions is to induce the apoptosis of tumor cells, but the antitumor mechanism is currently unclear. In the present study, we found that cell mortality and curcumin concentration were dose dependent. Curcumin of low concentrations (10 μ M) could reduce the level of reactive oxygen species (ROS) in tumor cells, while curcumin of high concentrations (80 μ M) was able to significantly increase the content of ROS. In addition, Western blotting detection suggested that curcumin of high concentrations can induce the release of Cyto-C and the activation of Caspase-3, and that ROS scavenger NAC apparently inhibits apoptosis protein release and activation, consequently slowing the curcumin-induced apoptosis. Taken together, curcumin further activates the mitochondrial apoptotic pathway by inducing cells to generate ROS and ultimately promotes the apoptosis of tumor cells.

[392]

TÍTULO / TITLE: - 2-Aminophenoxazine-3-one-induced apoptosis via generation of reactive oxygen species followed by c-jun N-terminal kinase activation in the human glioblastoma cell line LN229.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1456-66. doi: 10.3892/ijo.2013.2088. Epub 2013 Sep 4.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2088](#)

AUTORES / AUTHORS: - Che XF; Moriya S; Zheng CL; Abe A; Tomoda A; Miyazawa K

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Tokyo Medical University, Shinjuku-ku, Tokyo 160-8402, Japan.

RESUMEN / SUMMARY: - 2-Aminophenoxazine-3-one (Phx-3) induces apoptosis in several types of cancer cell lines. However, the mechanism of apoptosis induction by Phx-3 has not been fully elucidated. In this study, we investigated the anticancer effects of Phx-3 in the glioblastoma cell line LN229 and analyzed its molecular mechanism. The results indicated that 6- and 20-h treatment with Phx-3 significantly induced apoptosis in LN229 cells, with downregulation of survivin and XIAP. Both ERK and JNK, which are the members of the MAPK family, were activated after treatment with Phx-3. Inhibition of ERK using the specific inhibitor U0126 blocked the Phx-3-induced apoptosis only in part. However, inhibition of JNK using the specific inhibitor SP600125 completely prevented Phx-3-induced apoptosis and restored the phosphorylation states of ERK to the control levels. Enhanced generation of reactive oxygen species (ROS) was detected after 3-h treatment with Phx-3. In addition, the ROS scavenger melatonin almost completely blocked Phx-3-induced JNK activation and apoptosis. This suggests that JNK activation was mediated by Phx-3-induced ROS generation. Although SP600125 and melatonin completely blocked the reduction of mitochondrial membrane potential after a 3-h treatment with Phx-3, extension of Phx-3 exposure time to 20 h resulted in no cancelation of mitochondrial depolarization by these reagents. These reagents also had little effect on the decreased expression of survivin and XIAP during a 3-20-h exposure to Phx-3. These results indicate that the production of ROS following JNK activation is the main axis of Phx-3-induced apoptosis in LN229 cells for short-term exposure to Phx-3, whereas alternative mechanism(s) appear to be involved in apoptosis induction during long-term exposure to Phx-3.

[393]

TÍTULO / TITLE: - Pretreatment anti-Mullerian hormone predicts for loss of ovarian function after chemotherapy for early breast cancer.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 19. pii: S0959-8049(13)00564-9. doi: 10.1016/j.ejca.2013.07.014.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejca.2013.07.014

AUTORES / AUTHORS: - Anderson RA; Rosendahl M; Kelsey TW; Cameron DA

INSTITUCIÓN / INSTITUTION: - MRC Centre for Reproductive Health, University of Edinburgh, Queens Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK. Electronic address: richard.anderson@ed.ac.uk.

RESUMEN / SUMMARY: - AIM: Improving survival for women with early breast cancer (eBC) requires greater attention to the consequences of treatment, including risk to ovarian function. We have assessed whether biochemical markers of the ovarian reserve might improve prediction of chemotherapy related amenorrhoea. METHODS:

Women (n=59, mean age 42.6years [(range 23.3-52.5)] with eBC were recruited before any treatment. Pretreatment ovarian reserve markers (anti-Mullerian hormone [AMH], follicle-stimulating hormone [FSH], inhibin B) were analysed in relation to ovarian status at 2years. RESULTS: Pretreatment AMH was significantly lower in women with amenorrhoea at 2years (4.0+/-0.9pmol/L versus 17.2+/-2.5, P<0.0001), but FSH and inhibin B did not differ between groups. By logistic regression, pretreatment AMH, but not age, FSH or inhibin B, was an independent predictor of ovarian status at 2years (P=0.005; odds ratio 0.013). We combined these data with a similar cohort (combined n=75); receiver-operator characteristic analysis for AMH gave area under curve (AUC) of 0.90 (95% confidence interval (CI) 0.82-0.97)). A cross-validated classification tree analysis resulted in a binary classification schema with sensitivity 98.2% and specificity 80.0% for correct classification of amenorrhoea. CONCLUSION: Pretreatment AMH is a useful predictor of long term post chemotherapy loss of ovarian function in women with eBC, adding significantly to the only previously established individualising predictor, i.e. age. AMH measurement may assist decision-making regarding treatment options and fertility preservation procedures.

[394]

TÍTULO / TITLE: - Panic Disorder and Serotonin Reuptake Inhibitors Predict Coupling of Cortical and Cardiac Activity.

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

REVISTA / JOURNAL: - Neuropsychopharmacology. 2013 Aug 29. doi: 10.1038/npp.2013.224.

●● Enlace al texto completo (gratis o de pago) [1038/npp.2013.224](#)

AUTORES / AUTHORS: - Mueller EM; Panitz C; Nestoriuc Y; Stemmler G; Wacker J

INSTITUCIÓN / INSTITUTION: - Department of Psychology, Philipps-Universität Marburg, Marburg, Germany.

RESUMEN / SUMMARY: - Panic attacks, the cardinal symptom of panic disorder (PD), are characterized by intense physiological reactions including accelerated heart activity. Although cortical processes are thought to trigger and potentiate panic attacks, it is unknown whether individuals with PD have a general tendency to show elevated cortico-cardiac interactions, which could predispose them for brain-driven modulations of heart activity during panic. Consistent with this hypothesis, serotonin, a highly relevant neurotransmitter for panic and PD presumably affects the cortical control of the heart. The current study thus aimed to test whether PD and serotonin reuptake inhibitor (SRI) intake are related to cortico-cardiac interactions in the absence of acute panic. Human participants with PD (N=22), major depression (MD, clinical control group, N=21) or no psychiatric diagnosis (healthy control group, N=23) performed a gambling task. To measure cortico-cardiac coupling, the within-subject covariation of single-trial EEG after feedback presentation and subsequent changes in

heart period was determined. As in prior studies, there was a significant time-lagged covariation of EEG and heart activity indicating that trial-by-trial fluctuations of feedback-evoked EEG amplitude determined how much heart activity accelerated seconds later. Importantly, this covariation pattern was significantly potentiated in PD vs control participants. Moreover, concurrent SRI intake further augmented brain-heart covariation in individuals with PD and MD. The present findings demonstrate that PD and serotonin are associated with altered brain-heart interactions in a non-panic situation. Future work should clarify whether brain-heart coupling has a causal role in PD, for example by facilitating panic attacks. *Neuropsychopharmacology* advance online publication, 25 September 2013; doi:10.1038/npp.2013.224.

[395]

TÍTULO / TITLE: - Long-lasting inhibition of EGFR autophosphorylation in A549 tumor cells by intracellular accumulation of non-covalent inhibitors.

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

REVISTA / JOURNAL: - *Bioorg Med Chem Lett.* 2013 Oct 1;23(19):5290-4. doi: 10.1016/j.bmcl.2013.08.008. Epub 2013 Aug 11.

●● Enlace al texto completo (gratis o de pago) [1016/j.bmcl.2013.08.008](#)

AUTORES / AUTHORS: - Vacondio F; Carmi C; Galvani E; Bassi M; Silva C; Lodola A; Rivara S; Cavazzoni A; Alfieri RR; Petronini PG; Mor M

INSTITUCIÓN / INSTITUTION: - Dipartimento di Farmacia, Università degli Studi di Parma, Parco Area delle Scienze 27/a, I-43124 Parma, Italy.

RESUMEN / SUMMARY: - In the present study, a small set of reversible or irreversible 4-anilinoquinazoline EGFR inhibitors was tested in A549 cells at early (1h) and late (8h) time points after inhibitor removal from culture medium. A combination of assays was employed to explain the observed long-lasting inhibition of EGFR autophosphorylation. We found that EGFR inhibition at 8h can be due, besides to the covalent interaction of the inhibitor with Cys797, as for PD168393 (2) and its prodrug 4, to the intracellular accumulation of non-covalent inhibitors by means of an active cell uptake, as for 5 and 6. Compounds 5-6 showed similar potency and duration of inhibition of EGFR autophosphorylation as the covalent inhibitor 2, while being devoid of reactive groups forming covalent bonds with protein thiols.

[396]

TÍTULO / TITLE: - Significant association between cytotoxic T lymphocyte antigen 4 +49G>A polymorphism and risk of malignant bone tumors.

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

REVISTA / JOURNAL: - *Tumour Biol.* 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0908-7](#)

AUTORES / AUTHORS: - Yu F; Miao J

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, No. 98 Hospital of PLA, No.9 Chezhan Road, Huzhou, 313000, China, fengbinpla@126.com.

RESUMEN / SUMMARY: - Cytotoxic T lymphocyte antigen 4 (CTLA-4) gene +49G>A polymorphism was implicated to be associated with risk of malignant bone tumors, but the finding was inconclusive owing to the limited sample of a single study. The objective of the current study was to conduct a pooled analysis of four previously published studies to investigate the association between CTLA-4 +49G>A polymorphism and the risk of malignant bone tumors. Data were extracted, and the pooled odds ratio (OR) with the corresponding 95 % confidence interval (95 % CI) was calculated to assess the association. Those four published studies included a total of 2,165 subjects. The pooled results indicated that CTLA-4 +49G>A polymorphism was significantly associated with risk of malignant bone tumors (AA versus GG: OR = 2.24, 95 % CI 1.67-2.99, P < 0.001; AA/GA versus GG: OR = 1.35, 95 % CI 1.14-1.61, P = 0.001; AA versus GG/GA: OR = 2.00, 95 % CI 1.53-2.62, P < 0.001). Stratified analyses by tumor type showed that CTLA-4 +49G>A polymorphism was associated with risks of both osteosarcoma (AA versus GG: OR = 2.23, 95 % CI 1.45-3.43, P < 0.001; AA/GA versus GG: OR = 1.35, 95 % CI 1.04-1.75, P = 0.024; AA versus GG/GA: OR = 2.00, 95 % CI 1.34-2.98, P = 0.001) and Ewing's sarcoma (AA versus GG: OR = 2.24, 95 % CI 1.51-3.31, P < 0.001; AA/GA versus GG: OR = 1.36, 95 % CI 1.07-1.72, P = 0.011; AA versus GG/GA: OR = 2.01, 95 % CI 1.39-2.89, P < 0.001). Therefore, results from the current pooled analysis suggest that CTLA-4 +49G>A polymorphism is associated with risk of malignant bone tumors, including osteosarcoma and Ewing's sarcoma.

[397]

TÍTULO / TITLE: - Clinical and oncological effects of triplet chemotherapy followed by radical esophagectomy for resectable esophageal cancer associated with unfavorable prognostic factors.

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

REVISTA / JOURNAL: - Surg Today. 2013 Aug 21.

- [Enlace al texto completo \(gratis o de pago\) 1007/s00595-013-0700-8](#)

AUTORES / AUTHORS: - Shimoji H; Kinjo T; Karimata H; Nagahama M; Nishimaki T

INSTITUCIÓN / INSTITUTION: - Department of Digestive and General Surgery, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa, 903-0215, Japan, hshimoji@med.u-ryukyu.ac.jp.

RESUMEN / SUMMARY: - **PURPOSES:** The purpose of this study was to evaluate the hypothesis that the survival of patients undergoing R0 resection after triplet chemotherapy for resectable esophageal cancer with unfavorable prognostic factors (Category 3) would be similar to that of patients undergoing esophagectomy for esophageal cancer without such factors (Category 1). **METHODS:** Patients with

Category 3 tumors were assigned to receive triplet chemotherapy consisting of 5-fluorouracil, doxorubicin and nedaplatin (FAN) followed by radical esophagectomy. The outcomes of the bimodality treatment for Category 3 patients (n = 25) were compared with those of Category 1 patients (n = 41) in a prospective cohort study. RESULTS: Grade 3 or higher toxicity developed during chemotherapy in 32 % of the Category 3 patients, with no treatment-related deaths. No significant difference was detected in the surgery-related mortality and morbidity rates between the two groups. The recurrence-free survival was significantly worse in Category 3 than in Category 1 patients (p = 0.002), although the overall survival was not significantly different (p = 0.085) between the two groups in cases of R0 resection (5-year survival rates: 34.4 vs. 66.5 %). CONCLUSIONS: Although FAN chemotherapy followed by radical esophagectomy can be safely performed, this treatment modality may not have sufficient power to cure Category 3 disease.

[398]

TÍTULO / TITLE: - Prognostic implications of anaplastic lymphoma kinase gene aberrations in rhabdomyosarcoma; an immunohistochemical and fluorescence in situ hybridisation study.

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

REVISTA / JOURNAL: - J Clin Pathol. 2013 Aug 6. doi: 10.1136/jclinpath-2013-201655.

●● [Enlace al texto completo \(gratis o de pago\) 1136/jclinpath-2013-201655](#)

AUTORES / AUTHORS: - Lee JS; Lim SM; Rha SY; Roh JK; Cho YJ; Shin KH; Yang WI; Kim SH; Kim HS

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Yonsei University College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND: We investigated the diagnostic and prognostic usefulness of anaplastic lymphoma kinase (ALK) expression in Asian rhabdomyosarcoma (RMS) patients. PATIENTS AND METHODS: A total of 38 RMS tissue samples were collected over a 14-year period (1998-2012). ALK protein expression and gene copy number were analysed by immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH). RESULTS: Ten of the 38 RMS patients (26.3%) showed positive ALK protein expression. ALK protein expression was predominantly positive in alveolar RMS (ARMS) compared with embryonal RMS (ERMS) (80% vs 20%, p=0.03). ALK protein expression was statistically associated with ARMS histology, metastatic disease at diagnosis, and primary trunk site. In FISH analysis, no translocations were detected and ALK gene copy number gain was observed more frequently in ARMS than in ERMS (40% vs 17%). The ALK-positive group showed inferior overall survival (OS) compared with ALK-negative group (p=0.014) for both alveolar and embryonal RMS patients. In multivariate analysis, positive ALK expression was an independent prognostic factor for OS (p=0.02; HR, 3.1; 95% CI 1.2 to 8.3).

There was a significant strong positive correlation between ALK gene copy number and protein expression (Spearman's $r < 0.001$, $r = 0.77$). CONCLUSIONS: We demonstrated that ALK protein expression is statistically associated with ARMS histology, metastatic disease at diagnosis and primary trunk site. Additionally, ALK expression was an independent prognostic factor for worse survival. There was a strong correlation between IHC and FISH. Further studies are needed to evaluate the potential diagnostic and therapeutic role of ALK expression in RMS.

[399]

TÍTULO / TITLE: - HIV protease inhibitor Lopinavir induces apoptosis of primary effusion lymphoma cells via suppression of NF-kappaB pathway.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Sep 5. pii: S0304-3835(13)00642-3. doi: 10.1016/j.canlet.2013.08.045.

●● Enlace al texto completo (gratis o de pago) 1016/j.canlet.2013.08.045

AUTORES / AUTHORS: - Kariya R; Taura M; Suzu S; Kai H; Katano H; Okada S

INSTITUCIÓN / INSTITUTION: - Division of Hematopoiesis, Center for AIDS Research, Kumamoto University, 2-2-1, Honjo, Kumamoto 860-0811, Japan.

RESUMEN / SUMMARY: - Primary effusion lymphoma (PEL) is a non-Hodgkin lymphoma that occurs predominantly in patients with advanced AIDS. In this study, we examined the effect of HIV protease inhibitors, Lopinavir (LPV), Ritonavir (RTV) and Darunavir (DRV) on PEL cell lines in vitro and in vivo. LPV and RTV, but not DRV induced caspase-dependent apoptosis and suppressed NF-kappaB activity by inhibiting IKK phosphorylation in PEL cells. In a PEL xenograft mouse model, LPV significantly inhibited the growth and invasion of PEL cells. These results suggest that LPV may have promise for the treatment and prevention of PEL, which occurs in HIV/AIDS patients.

[400]

TÍTULO / TITLE: - Transferrin modified PEG-PLA-resveratrol conjugates: In vitro and in vivo studies for glioma.

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

REVISTA / JOURNAL: - Eur J Pharmacol. 2013 Sep 23. pii: S0014-2999(13)00687-0. doi: 10.1016/j.ejphar.2013.09.034.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejphar.2013.09.034

AUTORES / AUTHORS: - Guo W; Li A; Jia Z; Yuan Y; Dai H; Li H

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, The Affiliated Drum Tower Hospital of Nanjing University, Zhongshan Road, Nanjing 210008, China.

RESUMEN / SUMMARY: - Glioblastoma is one of the most malignant brain tumors with a poor prognosis. In this study, we examined the effects of transferrin (Tf)-modified poly

ethyleneglycol-poly lactic acid (PEG-PLA) nanoparticles conjugated with resveratrol (Tf-PEG-PLA-RSV) to glioma therapy in vitro and in vivo. The cell viability of Tf-PEG-PLA-RSV on C6 and U87 glioma cells was determined by the MTT assay. In vivo biodistribution and antitumor activity were investigated in Brain glioma bearing rat model of C6 glioma by i.p. administration of RSV-polymer conjugates. We found that the average diameter of each Tf-PEG-PLA-RSV is around 150nm with 32 molecules of Tf on surface. In vitro cytotoxicity of PEG-PLA-RSV against C6 and U87 cells was higher than that of free RSV, and further the modification of Tf enhanced the cytotoxicity of the RSV-polymer conjugates as a result of the increased cellular uptake of the RSV-modified conjugates by glioma cells. In comparison with free RSV, RSV conjugates could significantly decrease tumor volume and accumulate in brain tumor, which resulted in prolonging the survival of C6 glioma-bearing rats. These results suggest that Tf-NP-RSV had a potential of therapeutic effect to glioma both in vitro and in vivo and might be a potential candidate for targeted therapy of glioma and worthy of further investigation.

[401]

TÍTULO / TITLE: - Daidzein causes cytochrome c-mediated apoptosis via the Bcl-2 family in human hepatic cancer cells.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Oct;60:542-9. doi: 10.1016/j.fct.2013.08.022. Epub 2013 Aug 16.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.08.022](#)

AUTORES / AUTHORS: - Park HJ; Jeon YK; You DH; Nam MJ

INSTITUCIÓN / INSTITUTION: - Department of Biological Science, Gachon University, 534-2 Yeonsu-dong, Yeonsu-gu, Incheon 406-799, Republic of Korea.

RESUMEN / SUMMARY: - Daidzein, which belongs to the group of isoflavones from soybeans, has been extensively researched prostate, cervix, brain, breast, and colon cancer cell lines. However, daidzein has not been thoroughly investigated in human hepatic cancer cells; therefore, we investigated whether it inhibits hepatic cancer cell growth. Decreased cell proliferation was measured in daidzein-treated hepatic cancer cells (SK-HEP-1) upon real-time cell electronic sensing analysis however, it was not affected on normal human hepatocytes (Chang). Daidzein-induced apoptosis was demonstrated by comet and TUNEL assay. Moreover, we conducted two-dimensional electrophoresis to study the mechanism of daidzein-induced apoptosis in daidzein-treated SK-HEP-1 cells. Expression of peroxiredoxin-3 (Prdx-3), which modulates redox homeostasis of cells, was increased in protein analysis. Additionally, we measured the levels of reactive oxygen species and it was decreased in daidzein-treated SKHEP-1 cells. Daidzein-induced apoptosis in SK-HEP-1 cells was also associated with the up-regulation of Bak and down-regulation of Bcl-2 and Bcl-xL proteins. Moreover, daidzein

treatment increased in the release of mitochondrial cytochrome c and activation of APAF-1, caspase 9 and caspase 3. Overall, these results indicate that daidzein is a potent inducer of apoptosis in hepatic cancer cells via mitochondrial pathway.

[402]

TÍTULO / TITLE: - Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Sep 20.

●● [Enlace al texto completo \(gratis o de pago\) 1093/annonc/mdt378](#)

AUTORES / AUTHORS: - Hugen N; Verhoeven RH; Radema SA; de Hingh IH; Pruijt JF; Nagtegaal ID; Lemmens VE; de Wilt JH

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen.

RESUMEN / SUMMARY: - BACKGROUND: Colorectal mucinous adenocarcinoma (MC) has been associated with impaired prognosis compared with nonmucinous adenocarcinoma (NMC). Response to palliative chemotherapy is poor in metastatic disease, but the benefit of adjuvant chemotherapeutic treatment has never been assessed in large patient groups. This study analyses overall survival and efficacy of adjuvant chemotherapy in terms of survival in patients following radical resection for MC. PATIENTS AND METHODS: This population-based study involved 27 251 unselected patients diagnosed with colorectal carcinoma between 1990 and 2010 and recorded in a prospective pathology-based registry. Kaplan-Meier analysis and log-rank testing were used to estimate survival. Cox proportional hazard model was used to calculate multivariate hazard ratios for death. RESULTS: MC was found in 12.3% (N = 3052) of colorectal tumors with a different distribution compared with NMC, with 24.4% located in the rectum and 54.3% in the proximal colon (versus 38.0% and 30.6%), $P < 0.0001$. NMC was more often classified as stage I disease than MC (20.5% versus 10.9%), $P < 0.0001$. After adjustments for covariates, MC was associated with a higher risk of death only when located in the rectum [hazard ratio 1.22; 95% confidence interval (CI) 1.11-1.34]. Multivariate regression analysis showed a similar survival after adjuvant chemotherapy for stage III MC and NMC patients. CONCLUSIONS: The poor prognosis for MC is only present in rectal cancer. In the adjuvant setting, there is no difference in the efficacy of chemotherapy between MC and NMC; therefore, current adjuvant treatment recommendations should not take histology into account.

[403]

TÍTULO / TITLE: - Predicting response to anti-interleukin 12/23 treatment in psoriasis.

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

REVISTA / JOURNAL: - Br J Dermatol. 2013 Aug;169(2):240-1. doi: 10.1111/bjd.12405.

●● Enlace al texto completo (gratis o de pago) [1111/bjd.12405](#)

AUTORES / AUTHORS: - Wu KC; Reynolds NJ

INSTITUCIÓN / INSTITUTION: - Dermatological Sciences, Institute of Cellular Medicine, William Leech Building, Newcastle University, Newcastle Upon Tyne, NE2 4HH, U.K.

[404]

TÍTULO / TITLE: - Methylated-(3'')-Epigallocatechin Gallate Analog Suppresses Tumor Growth in Huh7 Hepatoma Cells Via Inhibition of Angiogenesis.

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

REVISTA / JOURNAL: - Nutr Cancer. 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) [1080/01635581.2013.783601](#)

AUTORES / AUTHORS: - Hashimoto O; Nakamura A; Nakamura T; Iwamoto H; Hiroshi M; Inoue K; Torimura T; Ueno T; Sata M

INSTITUCIÓN / INSTITUTION: - a Liver Cancer Division, Research Center for Innovative Cancer Therapy, Kurume University, Japan.

RESUMEN / SUMMARY: - It is agreed that many of the antitumor effects of (-)-epigallocatechin gallate (EGCG) are mediated by various other effects. We report a new finding, namely, the antiproliferation potential and mechanism of methylated-(3'')-epigallocatechin gallate analog (MethylEGCG) having a stronger anti-oxidation effect than EGCG. MethylEGCG inhibited activity of vascular endothelial growth factor (VEGF)-dependent VEGF receptor 2 and p42/44 MAPK, cell proliferation, and tube formation in human umbilical vascular endothelial cells (HUVECs) at 1 μ M. Even low-dose (1.1 mg/kg i.p. 8.3 mg/kg p.o.) administration suppressed tumor growth in xenografted Huh7 hepatoma mice by 50%. CD31 positive cells, visualized in blood vessels, were reduced in tumors by 18%, suggesting high antitumor activity via inhibition of angiogenesis. This study indicated that the modification of the 3'' position methylation of EGCG (MethylEGCG) could reduce cell growth effects at a low concentration in vivo.

[405]

TÍTULO / TITLE: - Association between the cytotoxic T-lymphocyte antigen 4 +49^a/G polymorphism and bladder cancer risk.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 8.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1152-x](#)

AUTORES / AUTHORS: - Wang L; Su G; Zhao X; Cai Y; Cai X; Zhang J; Liu J; Wang T; Wang J

INSTITUCIÓN / INSTITUTION: - Department of Urology, Zhengzhou Central Hospital, Zhengzhou University, Tongbai Road 195, Zhengzhou, 450000, China.

RESUMEN / SUMMARY: - Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is a potent immunoregulatory molecule that suppresses antitumor response by downregulating T cell activation. The most studied CTLA-4 +49^a/G polymorphism has been associated with various cancers risks. However, little is known about the association between CTLA-4 +49^a/G polymorphism and bladder cancer risk. A hospital-based case-control study was conducted in 300 patients with bladder cancer and 300 healthy controls matched with age and sex. The CTLA-4 +49^a/G polymorphism was genotyped using polymerase chain reaction-restriction fragment length polymorphism. Patients with bladder cancer had a significantly lower frequency of CTLA-4 +49GG genotype [odds ratio (OR) = 0.44, 95 % confidence interval (CI) = 0.23, 0.85; P = 0.01] and G allele (OR = 0.73, 95 % CI = 0.56, 0.96; P = 0.02) than healthy controls. When stratifying by the stage, grade, and histological type of bladder cancer, we found no statistical association. This is the first study to highlight the significant association between CTLA-4 +49^a/G polymorphism and bladder cancer risk. Additional studies are needed to confirm this finding.

[406]

TÍTULO / TITLE: - Inhibition of ATR kinase with the selective inhibitor VE-821 results in radiosensitization of cells of promyelocytic leukaemia (HL-60).

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

REVISTA / JOURNAL: - Radiat Environ Biophys. 2013 Aug 11.

●● Enlace al texto completo (gratis o de pago) [1007/s00411-013-0486-5](#)

AUTORES / AUTHORS: - Vavrova J; Zarybnicka L; Lukasova E; Rezacova M; Novotna E; Sinkorova Z; Tichy A; Pejchal J; Durisova K

INSTITUCIÓN / INSTITUTION: - Department of Radiobiology, Faculty of Health Sciences, University of Defence, Hradec Kralove, Brno, Czech Republic, vavrova@pmfhk.cz.

RESUMEN / SUMMARY: - We compared the effects of inhibitors of kinases ATM (KU55933) and ATR (VE-821) (incubated for 30 min before irradiation) on the radiosensitization of human promyelocyte leukaemia cells (HL-60), lacking functional protein p53. VE-821 reduces phosphorylation of check-point kinase 1 at serine 345, and KU55933 reduces phosphorylation of check-point kinase 2 on threonine 68 as assayed 4 h after irradiation by the dose of 6 Gy. Within 24 h after gamma-irradiation with a dose of 3 Gy, the cells accumulated in the G2 phase (67 %) and the number of cells in S phase decreased. KU55933 (10 μM) did not affect the accumulation of cells in G2 phase and did not affect the decrease in the number of cells in S phase after irradiation. VE-821 (2 and 10 μM) reduced the number of irradiated cells in the G2 phase to the level of non-irradiated cells and increased the number of irradiated cells in S phase, compared to irradiated cells not treated with inhibitors. In the 144 h

interval after irradiation with 3 Gy, there was a considerable induction of apoptosis in the VE-821 group (10 μ M). The repair of the radiation damage, as observed 72 h after irradiation, was more rapid in the group exposed solely to irradiation and in the group treated with KU55933 (80 and 77 % of cells, respectively, were free of DSBs), whereas in the group incubated with 10 μ M VE-821, there were only 61 % of cells free of DSBs. The inhibition of kinase ATR with its specific inhibitor VE-821 resulted in a more pronounced radiosensitizing effect in HL-60 cells as compared to the inhibition of kinase ATM with the inhibitor KU55933. In contrast to KU55933, the VE-821 treatment prevented HL-60 cells from undergoing G2 cell cycle arrest. Taken together, we conclude that the ATR kinase inhibition offers a new possibility of radiosensitization of tumour cells lacking functional protein p53.

[407]

TÍTULO / TITLE: - Association of Interleukin-12 Polymorphisms and Serum IL-12p40 Levels with Osteosarcoma Risk.

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

REVISTA / JOURNAL: - DNA Cell Biol. 2013 Oct;32(10):605-10. doi: 10.1089/dna.2013.2098. Epub 2013 Aug 30.

●● Enlace al texto completo (gratis o de pago) [1089/dna.2013.2098](http://dx.doi.org/10.1089/dna.2013.2098)

AUTORES / AUTHORS: - Wang J; Nong L; Wei Y; Qin S; Zhou Y; Tang Y

INSTITUCIÓN / INSTITUTION: - 1 Center of Clinical Laboratory, Affiliated Hospital of Youjiang Medical College for Nationalities, Baise, China.

RESUMEN / SUMMARY: - No previous studies reported the association of IL-12 polymorphisms with osteosarcoma. We aimed to investigate the association in a Chinese population. IL-12^a rs568408, rs2243115, and IL-12B rs3212227 polymorphisms were evaluated in a case-control study of 106 osteosarcoma patients and 210 health controls by using polymerase chain reaction-restriction fragment length polymorphism. Serum IL-12p40 levels were measured by enzyme-linked immunosorbent assay. The serum IL-12p40 levels were significantly higher in controls than those in osteosarcoma patients ($p < 0.01$). Genotypes of rs568408 GA and GA/AA, and rs3212227 CC and AC/CC were associated with the risk of osteosarcoma (rs568408 GA: odds ratios [OR]=1.86, 95% confidence intervals [CI]=1.11-3.12; GA/AA: OR=1.75, 95% CI=1.06-2.89, and rs3212227 CC: OR=2.70, 95% CI=1.38-5.28; CC/AC: OR=1.73, 95% CI=1.03-2.90). Moreover, rs3212227 CC/AC genotypes were significantly associated with decreased serum IL-12p40 levels in osteosarcoma patients compared to AA genotypes ($p = 0.035$). Stratification analysis showed no associations between rs3212227 variant and the patients' gender, tumor location, and metastasis. Our data suggest that the serum IL-12p40 levels associate with the risk of osteosarcoma and are regulated by IL-12B rs3212227 polymorphism. The IL-12^a rs568408 and IL-12B rs3212227 may confer the susceptibility to osteosarcoma risk.

[408]

TÍTULO / TITLE: - Induction of apoptosis by c9, t11-CLA in human endometrial cancer RL 95-2 cells via ERalpha-mediated pathway.

RESUMEN / SUMMARY: -

ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23954748

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

1016/j.chemphyslip.2013.07.009

AUTORES / AUTHORS: - Wang J; Liu X; Zhang X; Liu J; Ye S; Xiao S; Chen H; Wang H

INSTITUCIÓN / INSTITUTION: - Liaoning Key Laboratory of Food Biological Technology, School of Food Science and Technology, Dalian Polytechnic University, 116034 Dalian, China.

RESUMEN / SUMMARY: - Numerous studies have shown that conjugated linoleic acid (CLA) can inhibit cancer cells growth and induce apoptosis in vitro and in vivo. The aim of the present study was to investigate the effects of CLA, including cis9, trans11-conjugated linoleic acid (c9, t11-CLA) and trans10, cis12-conjugated linoleic acid (t10, c12-CLA), on apoptosis of human endometrial cancer RL 95-2 cells and its related mechanisms. The MTT analysis was used to evaluate the effect of CLA isomers on the viability of endometrial cancer RL 95-2 cells. We then estimated the apoptosis by Morphological observation and Annexin V-FITC/PI staining and flow cytometry. We also used Western blot analysis to assess the expression of caspase-3, Bax, Bcl-2 proteins and the activation of Akt/p-Akt and ERalpha/p-ERalpha. Propylpyrazole-triol (PPT), a selective ERalpha agonist was used to confirm the induction of apoptosis by c9, t11 CLA may relate to ERalpha-mediated pathway. In CLA-treated RL 95-2 cells, we found that c9, t11-CLA inhibited viability and triggered apoptosis, as judged from nuclear morphology and flow cytometric analysis. The expression of caspase-3 and the ratio of Bax/Bcl-2 were significant increased, but no obvious change was observed about Akt and p-Akt in c9, t11-CLA-treated cells. However, the expression of total ERalpha level in RL 95-2 cells-treated with c9, t11-CLA was unchanged, while in the concentration of 80mM, c9, t11-CLA down-regulated the protein expression level of p-ERalpha. Then PPT has the antagonistic action on growth inhibitory effect in RL 95-2 cells incubated with c9, t11-CLA. This study demonstrated that c9, t11- CLA could induce apoptosis in RL 95-2 cells, and may involve in ERalpha-mediated pathway. These results indicated that c9, t11- CLA could induce apoptosis of endometrial cancer cells and may be potential agents for the treatment of endometrial cancer.

[409]

TÍTULO / TITLE: - Evading apoptosis in cancer.

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

REVISTA / JOURNAL: - Trends Cell Biol. 2013 Aug 16. pii: S0962-8924(13)00117-7. doi: 10.1016/j.tcb.2013.07.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.tcb.2013.07.006](https://doi.org/10.1016/j.tcb.2013.07.006)

AUTORES / AUTHORS: - Fernald K; Kurokawa M

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Toxicology, Geisel School of Medicine at Dartmouth, Hanover, NH 03755, USA.

RESUMEN / SUMMARY: - Carcinogenesis is a mechanistically complex and variable process with a plethora of underlying genetic causes. Cancer development comprises a multitude of steps that occur progressively starting with initial driver mutations leading to tumorigenesis and, ultimately, metastasis. During these transitions, cancer cells accumulate a series of genetic alterations that confer on the cells an unwarranted survival and proliferative advantage. During the course of development, however, cancer cells also encounter a physiologically ubiquitous cellular program that aims to eliminate damaged or abnormal cells: apoptosis. Thus, it is essential that cancer cells acquire instruments to circumvent programmed cell death. Here we discuss emerging evidence indicating how cancer cells adopt various strategies to override apoptosis, including amplifying the antiapoptotic machinery, downregulating the proapoptotic program, or both.

[410]

TÍTULO / TITLE: - JWA suppresses tumor angiogenesis via Sp1-activated MMP-2 and its prognostic significance in human gastric cancer.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt311](https://doi.org/10.1093/carcin/bgt311)

AUTORES / AUTHORS: - Chen Y; Huang Y; Huang Y; Xia X; Zhang J; Zhou Y; Tan Y; He S; Qiang F; Li A; Roe OD; Li G; Zhou J

INSTITUCIÓN / INSTITUTION: - Department of Molecular Cell Biology and Toxicology, Key Lab of Modern Toxicology (NJMU), Ministry of Education; Jiangsu Key Lab of Cancer Biomarkers, Prevention & Treatment, Cancer Center; School of Public Health, Nanjing Medical University, 140 Hanzhong Road, Nanjing 210029, People's Republic of China.

RESUMEN / SUMMARY: - JWA, a multifunctional microtubule-binding protein, plays an important role in regulating tumor metastasis via inhibition of MMP-2. Recent investigations suggest that MMP-2 is an angiogenesis associated molecule. In this study, we provide novel evidence that JWA inhibits tumor angiogenesis in gastric cancer (GC). In two independent retrospective GC cohorts, we found that the expression of JWA was downregulated and MMP-2 was upregulated in gastric cancerous tissues compared with normal gastric mucosa. For patients treated with surgery alone a strong and independent negative prognostic value was shown for low JWA and high MMP-2 expression separately, but even stronger when combined (HR =

7.75, $P < 0.001$ in the training cohort; HR = 2.31, $P < 0.001$ in the validation cohort). Moreover we found that loss of JWA expression strongly correlated to enhanced GC angiogenesis. In vitro, JWA inhibited MMP-2 at both mRNA and protein level through modulating Sp1 activity. Knockdown of endogenous JWA resulted in enhanced HUVECs tube formation and MMP-2 expression. Furthermore, JWA was found to inhibit Sp1 activity via an ubiquitin-proteasome-dependent mechanism and downregulate the proangiogenic MMP-2 expression; JWA also via TIMP2 inhibited MMP-2 expression. Our findings imply that JWA and MMP-2 may serve as promising prognostic markers in resectable gastric cancer and JWA as biomarker of angiogenesis in GC and a therapeutic target by MMP-2 modulation.

[411]

TÍTULO / TITLE: - Matrine induction of reactive oxygen species activates p38 leading to caspase-dependent cell apoptosis in non-small cell lung cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2529-35. doi: 10.3892/or.2013.2727. Epub 2013 Sep 9.

●● Enlace al texto completo (gratuito o de pago) [3892/or.2013.2727](#)

AUTORES / AUTHORS: - Tan C; Qian X; Jia R; Wu M; Liang Z

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Soochow University, Suzhou, Jiangsu 215123, P.R. China.

RESUMEN / SUMMARY: - Non-small cell lung carcinoma (NSCLC) is one of the most refractory cancers in the clinic; it is insensitive to chemotherapy and is usually excised. However, screening natural compounds from herbs is also considered a possible method for its therapy. In the present study, we investigated whether matrine, a natural compound isolated from *Sophora flavescens* Ait. and exerting an inhibitory effect on lung cancer cells, also indicates inhibition on NSCLC cells and elucidated its molecular mechanism. Firstly, it is confirmed that matrine induces apoptosis of human NSCLC cells with anti-apoptotic factors inhibited and dependent on caspase activity. In addition, we found that matrine increases the phosphorylation of p38 but not its total protein, and inhibition of the p38 pathway with SB202190 partially prevents matrine-induced apoptosis. Furthermore, matrine generates reactive oxygen species (ROS) in a dose- and time-dependent manner, which is reversed by pretreatment with N-acetyl-L-cysteine (NAC). Additionally, inhibition of cell proliferation and increase of phosphorylation of p38 was also partially reversed by NAC. Collectively, matrine activates p38 pathway leading to a caspase-dependent apoptosis by inducing generation of ROS in NSCLC cells and may be a potential chemical for NSCLC.

[412]

TÍTULO / TITLE: - MicroRNA Hsa-miR-125^a-3p Activates p53 and Induces Apoptosis in Lung Cancer Cells.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Oct;31(8):538-544. Epub 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.820314](#)

AUTORES / AUTHORS: - Jiang L; Chang J; Zhang Q; Sun L; Qiu X

INSTITUCIÓN / INSTITUTION: - Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, Liaoning, China,1.

RESUMEN / SUMMARY: - The mature microRNA hsa-miR-125^a-3p is derived from the 3' end of pre-miR-125^a. Here, we reported that hsa-miR-125^a-3p suppressed proliferation and induced apoptosis in A549 cells. In addition, wild-type p53 mRNA and protein expression was increased by hsa-miR-125^a-3p over-expression. Moreover, blocking wild-type p53 attenuated the effect of hsa-miR-125^a-3p on apoptosis but could not restore completely. In p53-deficient cell line H1299, hsa-miR-125^a-3p still induced apoptosis. Taken together, these data suggest that hsa-miR-125^a-3p induces apoptosis not only via the p53 pathway in human lung cancer cells. These results provide new insight into the roles of the miR-125^a family in lung cancer.

[413]

TÍTULO / TITLE: - Valproic acid inhibits the growth of HeLa cervical cancer cells via caspase-dependent apoptosis.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Sep 20. doi: 10.3892/or.2013.2747.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2747](#)

AUTORES / AUTHORS: - Han BR; You BR; 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: - Valproic acid (VPA) as a histone deacetylase (HDAC) inhibitor has an anticancer effect. In the present study, we evaluated the effects of VPA on the growth and death of HeLa cervical cancer cells in relation to reactive oxygen species (ROS) and glutathione (GSH). Dose- and time-dependent growth inhibition was observed in HeLa cells with an IC₅₀ of approximately 10 mM at 24 h. DNA flow cytometric analysis indicated that 10 mM VPA induced a G2/M phase arrest of the cell cycle. This agent also induced apoptosis, which was accompanied by the cleavage of PARP, the activation of caspase-3, -8 and -9, and the loss of mitochondrial membrane potential (MMP; Psim). All the tested caspase inhibitors significantly prevented HeLa apoptotic cell death induced by VPA, whereas TNF-α intensified the apoptotic cell death. With respect to ROS and GSH levels, VPA increased ROS levels and induced GSH

depletion. However, N-acetyl cysteine (NAC; an antioxidant) and L-buthionine sulfoximine (BSO; a GSH synthesis inhibitor) did not significantly affect cell death in VPA-treated HeLa cells. In conclusion, VPA inhibits the growth of HeLa cervical cancer cells via caspase-dependent apoptosis and the growth inhibition is independent of ROS and GSH level changes.

[414]

TÍTULO / TITLE: - Inhibition of LDH-A by oxamate induces G2/M arrest, apoptosis and increases radiosensitivity in nasopharyngeal carcinoma cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Sep 19. doi: 10.3892/or.2013.2735.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2735](#)

AUTORES / AUTHORS: - Zhai X; Yang Y; Wan J; Zhu R; Wu Y

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, The First Affiliated Hospital, Soochow University, Suzhou, P.R. China.

RESUMEN / SUMMARY: - An elevated rate of glucose consumption and the dependency on aerobic glycolysis for ATP generation have long been observed in cancer cells, a phenomenon known as the Warburg effect. The altered energy metabolism in cancer cells provides an attractive opportunity for developing novel cancer therapeutic strategies. Lactate dehydrogenase (LDH), which catalyzes the transformation of pyruvate to lactate, plays a vital role in the process of glycolysis. It has been reported that the level of LDH-A expression is increased both in head and neck cancer cells and in the blood serum of nasopharyngeal carcinoma (NPC) patients, and is associated with poor prognosis. However, the effect of LDH-A inhibition on NPC cells remains unknown. Here, in the present study, we found that oxamate, a classical inhibitor of LDH-A, suppressed cell proliferation in a dose- and time-dependent manner both in CNE-1 and CNE-2 cells, two NPC cancer cell lines. LDH inhibition by oxamate induced G2/M cell cycle arrest via downregulation of the CDK1/cyclin B1 pathway and promoted apoptosis through enhancement of mitochondrial ROS generation. N-acetylcysteine, a specific scavenger of ROS, significantly blocked the growth inhibition effect induced by oxamate. We also identified that oxamate increased sensitivity to ionizing radiation in the two NPC cancer cell lines. Furthermore, we verified similar results in tumor xenograft models. Collectively, these results suggest that LDH-A may serve as a promising therapeutic target for NPC treatment.

[415]

TÍTULO / TITLE: - Arsenic disulfide induces apoptosis of human diffuse large B cell lymphoma cells involving Bax cleavage.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2427-34. doi: 10.3892/or.2013.2729. Epub 2013 Sep 10.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2729](https://doi.org/10.3892/or.2013.2729)

AUTORES / AUTHORS: - Wang L; Liu X; Li X; Lv X; Lu K; Chen N; Li P; Wang X

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, P.R. China.

RESUMEN / SUMMARY: - The aim of the present study was to investigate the effect of arsenic disulfide (As₂S₂) on the proliferation and apoptosis of LY1 and LY8 human diffuse large B cell lymphoma (DLBCL) cells in an attempt to discover a more effective alternative therapy scheme. Human DLBCL cells LY1 and LY8 were treated with various concentrations of As₂S₂ for different time periods. Cell viability was detected by the CCK-8 assay; cell apoptosis was evaluated by flow cytometric analysis. The expression levels of Bax, Bcl-2 and caspase-3 were examined by quantitative PCR and western blotting. We found that the DLBCL cell viability was significantly decreased following treatment with As₂S₂ for 24, 48 and 72 h. Along with increasing As₂S₂ concentrations, the DLBCL cell viability was notably reduced when compared with the control group, and the results were statistically significant. Meanwhile, the apoptotic rates of DLBCL cells were significantly enhanced at 24, 48 and 72 h following treatment with increasing As₂S₂ concentration, and the results were also statistically significant. The quantitative PCR results showed that at the mRNA level, the Bax/Bcl-2 expression ratio was increased and caspase-3 mRNA expression was upregulated in As₂S₂-treated DLBCL cells. Western blot analysis revealed that at the protein level, As₂S₂ increased the Bax/Bcl-2 protein ratio in contrast to decreased pro-caspase-3 expression in the DLBCL cells. Our findings also demonstrated that 21-kDa Bax was proteolytically cleaved into the 18-kDa Bax in the DLBCL cells exposed to As₂S₂ at a concentration of 10 microM. As₂S₂ inhibited proliferation and induced apoptosis of LY1 and LY8 cells in a concentration- and time-dependent manner. The effect was partly due to the induction of mitochondrial-dependent apoptosis involving Bax cleavage.

[416]

TÍTULO / TITLE: - Phase I study of azacitidine and bortezomib in adults with relapsed or refractory acute myeloid leukemia.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Aug 16.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.833333](https://doi.org/10.3109/10428194.2013.833333)

AUTORES / AUTHORS: - Walker AR; Klisovic RB; Garzon R; Schaaf LJ; Humphries K; Devine SM; Byrd JC; Grever MR; Marcucci G; Blum W

RESUMEN / SUMMARY: - Abstract We previously reported that bortezomib indirectly modulates transcription of DNA methyltransferase 1 (DNMT). We designed a phase I study of azacitidine (a direct DNMT inhibitor) plus bortezomib in acute myeloid

leukemia (AML) to determine safety and tolerability. Twenty-three adults with relapsed/refractory AML received azacitidine 75mg/m² daily on days 1-7. Bortezomib was dose escalated from 0.7mg/m² on days 2 and 5 to 1.3mg/m² on days 2, 5, 9, and 12. The target dose was reached without dose limiting toxicities. Infection and/or febrile neutropenia were frequent. Patients received a median of 2 cycles of therapy (range, 1-12+). Five of 23 patients achieved remission including two with morphologic and cytogenetic complete response (CR) and three with CR and incomplete count recovery (CRI). Of CR/CRI responders with cytogenetic abnormalities at baseline, three of four achieved cytogenetic CR. The combination of azacitidine and bortezomib was tolerable and active in this cohort of poor-risk previously-treated AML patients.

[417]

TÍTULO / TITLE: - Down-Regulation of Stromal Caveolin-1 Expression in Esophageal Squamous Cell Carcinoma: A Potent Predictor of Lymph Node Metastases, Early Tumor Recurrence, and Poor Prognosis.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3225-x](#)

AUTORES / AUTHORS: - Jia Y; Wang N; Wang J; Tian H; Ma W; Wang K; Tan B; Zhang G; Yang S; Bai B; Cheng Y

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Qilu Hospital of Shandong University, Jinan, Shandong, People's Republic of China.

RESUMEN / SUMMARY: - **BACKGROUND:** Recent studies have identified loss of stromal caveolin-1 (Cav-1) expression as a new prognostic histological characteristic in various types of human cancers. However, the clinical and pathological significance of stromal Cav-1 expression in esophageal squamous cell carcinoma (ESCC) remains largely unknown. We examined Cav-1 expression in both tumor and stromal cells in ESCC tissue by immunohistochemical analysis to evaluate its clinicopathological significance and prognostic value. **METHODS:** A total of 110 patients with ESCC who underwent surgical resection were included in this study. The expression of Cav-1 in both tumor and stromal cells in esophageal tumor tissues was examined immunohistochemically. **RESULTS:** Cav-1 expression was found in the cytoplasm of both tumor and stromal cells. Tumor Cav-1 overexpression was observed in 37.3 % tumors, which correlated to deeper tumor invasion ($p = 0.038$). Down-regulation of stromal Cav-1 expression was observed in 40.9 % tumors. The stromal Cav-1 down-regulation group had more lymph node metastases and more locoregional recurrences than those with higher expression ($p = 0.020$ and $p = 0.002$, respectively). In addition, down-regulation of stromal Cav-1 expression was associated with shorter disease-free survival ($p < 0.001$) and overall survival ($p < 0.001$). Multivariate analysis revealed that down-regulation of stromal Cav-1 expression was an independent prognostic factor for both disease-free survival

($p = 0.028$) and overall survival ($p = 0.007$). CONCLUSIONS: Down-regulation of stromal Cav-1 expression in ESCC had high malignant potential. It predicts high-risk of lymph node metastases and locoregional recurrence, and it could be a powerful prognostic marker for patients with ESCC.

[418]

TÍTULO / TITLE: - Role of the renin-angiotensin-aldosterone system and the glutathione S-transferase Mu, Pi and Theta gene polymorphisms in cardiotoxicity after anthracycline chemotherapy for breast carcinoma.

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

REVISTA / JOURNAL: - Int J Biol Markers. 2013 Aug 30:0. doi: 10.5301/jbm.5000041.

●● Enlace al texto completo (gratis o de pago) [5301/jbm.5000041](#)

AUTORES / AUTHORS: - Vivenza D; Feola M; Garrone O; Monteverde M; Merlano M; Lo Nigro C

INSTITUCIÓN / INSTITUTION: - 1 Laboratory of Cancer Genetics and Translational Oncology, Oncology Division S. Croce General Hospital, Cuneo - Italy.

RESUMEN / SUMMARY: - **Background:** Anthracyclines are among the most active drugs against breast cancer, but can exert cardiotoxic effects eventually resulting in congestive heart failure (CHF). Identifying breast cancer patients at high risk of developing cardiotoxicity after anthracycline therapy would be of value in guiding the use of these agents. **Aims:** We determined whether polymorphisms in the renin-angiotensin-aldosterone system (RAAS) and in the glutathione S-transferase (GST) family of phase II detoxification enzymes might be useful predictors of left ventricular ejection fraction (LVEF) kinetics and risk of developing CHF. We sought correlations between the development of cardiotoxicity and gene polymorphisms in 48 patients with early breast cancer treated with adjuvant anthracycline chemotherapy. **Methods:** We analyzed the following polymorphisms: p.Met235Thr and p.Thr174Met in angiotensinogen (*AGT*), Ins/Del in angiotensin-converting enzyme (*ACE*), A1166C in angiotensin II type-1 receptor (*AGTR1A*), c.-344T>C in aldosterone synthase (*CYP11B2*), p.Ile105Val in *GSTP1*. Additionally, we analyzed the presence or absence of the *GSTT1* and *GSTP1* genes. A LVEF $\leq 50\%$ was detected at least once during the 3 years of follow-up period in 13 out of 48 patients (27.1%). **Conclusion:** RAAS gene polymorphisms were not significantly associated with the development of cardiotoxicity. *GSTM1* may be useful as a biomarker of higher risk of cardiotoxicity, as demonstrated in our cohort of patients ($p=0.147$).

[419]

TÍTULO / TITLE: - Induction of apoptosis and inhibition of invasion in choriocarcinoma JEG-3 cells by alpha-calendic acid and beta-calendic acid.

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

REVISTA / JOURNAL: - Prostaglandins Leukot Essent Fatty Acids. 2013 Aug 14. pii: S0952-3278(13)00136-1. doi: 10.1016/j.plefa.2013.06.007.

●● Enlace al texto completo (gratis o de pago) 1016/j.plefa.2013.06.007

AUTORES / AUTHORS: - Li Q; Wang H; Ye S; Xiao S; Xie Y; Liu X; Wang J

INSTITUCIÓN / INSTITUTION: - Liaoning Key Laboratory of Food Biological Technology, School of Food Science and Technology, Dalian Polytechnic University, No. 1 Qinggongyuan, Gan District, Dalian 116034, China.

RESUMEN / SUMMARY: - Alfa-calendic acid and beta-calendic acid, geometric and positional isomers of linolenic acid were previously shown to possess potent anticancer properties. In this study, we found that alpha-calendic acid and beta-calendic acid could induce apoptosis and suppress invasion of human choriocarcinoma JEG-3 cells in vitro. Treatment with alpha-calendic acid and beta-calendic acid significantly increased oxidative stress in human choriocarcinoma JEG-3 cells detected by the level of reactive oxygen species (ROS), lipid peroxidation production malondialdehyde (MDA), glutathione (GSH) and the effects of antioxidants NAC and alpha-tocopherol. Furthermore, oxidative stress activated the phosphorylation of p38MAPK. SB203580, a selective p38MAPK inhibitor, blocked the apoptosis induced by alpha-calendic acid and beta-calendic acid by upregulating Bcl-2/Bax ratio and inhibition of the activation of Caspase-3 and Caspase-9. SB20350 also partially abrogated the cell invasion effects of alpha-calendic acid and beta-calendic acid. These results suggested that alpha-calendic acid and beta-calendic acid induced apoptosis and inhibited invasion in JEG-3 cells by activation of oxidative stress pathways and subsequent activation of P38MAPK.

[420]

TÍTULO / TITLE: - Molecular Imaging of Apoptosis for Early Prediction of Therapy Efficiency.

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

REVISTA / JOURNAL: - Curr Pharm Des. 2013 Sep 11.

AUTORES / AUTHORS: - De Saint-Hubert M; Bauwens M; M Mottaghy F

INSTITUCIÓN / INSTITUTION: - Cardiovascular Research Institute Maastricht (CARIM), MUMC+, Maastricht, The Netherlands. Marijke.De.SaintHubert@mumc.nl.

RESUMEN / SUMMARY: - Evasion of apoptosis is one of the hallmarks of cancer and any effective therapy primarily attempts to induce apoptosis. The evaluation of the degree of success of cancer therapy is currently mainly based on clinical and laboratory

parameters and in a later stage on tumor shrinkage. However, none of these parameters provide an objective and early analysis of a therapeutic effect. Molecular imaging may provide a tool for this purpose by using not only pathophysiological but also biochemical effects of the therapy. First in the field, FDG-PET has been explored and demonstrated to offer insight in the amount of viable cells, even though false positives are common due to the lack of specificity of this particular radiopharmaceutical. More specific markers target the dying cells instead of those remaining alive. Specific apoptosis markers have been developed of which the radiolabeled Annexin A5 is the most intensely studied probe. Site-specific labeling strategies have improved this imaging probe with good results both in pre-clinical studies and in clinical trials, with promises for clinical applications. Caspase sensitive probes, such as the isatines, can also effectively image apoptosis but are limited due to the high background activities. More recent discoveries of small apoptosis sensitive probes, such as ¹⁸F-ML10, are currently being explored. In this review, the most important apoptosis sensitive probes are described from both a pre-clinical and a clinical perspective, highlighting their potential but also their limitations as an early marker for therapeutic success. It seems that apoptosis imaging can help to guide therapy, not by replacing the current methodology but by providing additional and useful information.

[421]

TÍTULO / TITLE: - Terfenadine induces anti-proliferative and apoptotic activities in human hormone-refractory prostate cancer through histamine receptor-independent Mcl-1 cleavage and Bak up-regulation.

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

REVISTA / JOURNAL: - Naunyn Schmiedeberg's Arch Pharmacol. 2013 Sep 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00210-013-0912-x](#)

AUTORES / AUTHORS: - Wang WT; Chen YH; Hsu JL; Leu WJ; Yu CC; Chan SH; Ho YF; Hsu LC; Guh JH

INSTITUCIÓN / INSTITUTION: - School of Pharmacy, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, 100, Taiwan.

RESUMEN / SUMMARY: - Although the results of several studies have underscored the regulatory effect of H1-histamine receptors in cell proliferation of some cancer cell types, its effect in prostate cancers remains unclear. We have therefore studied the effect of terfenadine (an H1-histamine receptor antagonist) in prostate cancer cell lines. Our data demonstrate that terfenadine was effective against PC-3 and DU-145 cells (two prostate cancer cell lines). In contrast, based on the sulforhodamine B assay, loratadine had less potency while fexofenadine and diphenhydramine had little effect. Terfenadine induced the cleavage of Mcl-1 cleavage into a pro-apoptotic 28-kDa fragment and up-regulation of Bak, resulting in the loss of mitochondrial membrane

potential (DeltaPsim) and the release of cytochrome c and apoptosis-inducing factor into the cytosol. The activation of caspase cascades was detected to be linked to terfenadine action. Bak up-regulation was also examined at both the transcriptional and translational levels, and Bak activation was validated based on conformational change to expose the N terminus. Terfenadine also induced an indirect-but not direct-DNA damage response through the cleavage and activation of caspase-2, phosphorylation and activation of Chk1 and Chk2 kinases, phosphorylation of RPA32 and acetylation of Histone H3; these processes were highly correlated to severe mitochondrial dysfunction and the activation of caspase cascades. In conclusion, terfenadine induced apoptotic signaling cascades against HRPCs in a sequential manner. The exposure of cells to terfenadine caused the up-regulation and activation of Bak and the cleavage of Mcl-1, leading to the loss of DeltaPsim and activation of caspase cascades which further resulted in DNA damage response and cell apoptosis.

[422]

TÍTULO / TITLE: - Sigma 1 Receptor plays a prominent role in IL-24-induced cancer-specific apoptosis.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 20;439(2):215-20. doi: 10.1016/j.bbrc.2013.08.057. Epub 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.08.057

AUTORES / AUTHORS: - Do W; Herrera C; Mighty J; Shumskaya M; Redenti SM; Sauane M

INSTITUCIÓN / INSTITUTION: - Department of Biological Sciences, Herbert H. Lehman College, City University of New York, 250 Bedford Park Boulevard West, Bronx, NY 10468, United States.

RESUMEN / SUMMARY: - Interleukin-24 (IL-24), a member of the IL-10 cytokine family, is an immunomodulatory cytokine that also displays broad cancer-specific suppressor effects. The tumor suppressor activities of IL-24 include inhibition of angiogenesis, sensitization to chemotherapy, and cancer-specific apoptosis. We show that Sigma 1 Receptor (S1R), a ligand-regulated protein chaperone contributes to IL-24 induction of apoptosis. IL-24 generated from an adenovirus expressing IL-24 (Ad.IL-24) induces cancer-specific apoptosis by inducing an endoplasmic reticulum (ER) stress, reactive oxygen species production, and calcium mobilization. The present studies reveals that S1R is required for Ad.IL-24-induced cell death. We provide several lines of evidence to confirm a physical and functional interaction between IL-24 and S1R including: (a) S1R and IL-24 co-localize, as judged by immunocytochemical analysis studies; (b) S1R and IL-24 co-immunoprecipitate using either S1R or IL-24 antibody; (c) S1R agonist (+)-SKF10047 inhibits apoptosis by Ad.IL-24; (d) (+)-SKF10047-mediated inhibition of Ad.IL-24 results in: diminished ER stress protein expression; (e) Calcium mobilization; and (f) ROS production. Collectively, these data demonstrate that S1R interacts with IL-24 and

suggest that IL-24:S1R interaction determines apoptosis induction by Ad.IL-24. These studies define Sigma 1 Receptor as a key initial mediator of IL-24 induction of cancer-specific killing. These findings have important implications for our understanding of IL-24 as a tumor suppressor protein as well as an immune modulating cytokine.

[423]

TÍTULO / TITLE: - 3,5,4'-Trimethoxystilbene, a natural methoxylated analog of resveratrol, inhibits breast cancer cell invasiveness by downregulation of PI3K/Akt and Wnt/beta-catenin signaling cascades and reversal of epithelial-mesenchymal transition.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Aug 3;272(3):746-756. doi: 10.1016/j.taap.2013.07.019.

●● Enlace al texto completo (gratis o de pago) 1016/j.taap.2013.07.019

AUTORES / AUTHORS: - Tsai JH; Hsu LS; Lin CL; Hong HM; Pan MH; Way TD; Chen WJ

INSTITUCIÓN / INSTITUTION: - Institute of Biochemistry and Biotechnology, Chung Shan Medical University, Taichung 402, Taiwan, ROC.

RESUMEN / SUMMARY: - The molecular basis of epithelial-mesenchymal transition (EMT) functions as a potential therapeutic target for breast cancer because EMT may endow breast tumor-initiating cells with stem-like characteristics and enable the dissemination of breast cancer cells. We have recently verified the antitumor activity of 3,5,4'-trimethoxystilbene (MR-3), a naturally methoxylated derivative of resveratrol, in colorectal cancer xenografts via an induction of apoptosis. The effect of MR-3 on EMT and the invasiveness of human MCF-7 breast adenocarcinoma cell line were also explored. We found that MR-3 significantly increased epithelial marker E-cadherin expression and triggered a cobblestone-like morphology of MCF-7 cells, while reciprocally decreasing the expression of mesenchymal markers, such as snail, slug, and vimentin. In parallel with EMT reversal, MR-3 downregulated the invasion and migration of MCF-7 cells. Exploring the action mechanism of MR-3 on the suppression of EMT and invasion indicates that MR-3 markedly reduced the expression and nuclear translocation of beta-catenin, accompanied with the downregulation of beta-catenin target genes and the increment of membrane-bound beta-catenin. These results suggest the involvement of Wnt/beta-catenin signaling in the MR-3-induced EMT reversion of MCF-7 cells. Notably, MR-3 restored glycogen synthase kinase-3beta activity by inhibiting the phosphorylation of Akt, the event required for beta-catenin destruction via a proteasome-mediated system. Overall, these findings indicate that the anti-invasive activity of MR-3 on MCF-7 cells may result from the suppression of EMT via down-regulating phosphatidylinositol 3-kinase (PI3K)/AKT signaling, and consequently, beta-catenin nuclear translocation. These occurrences ultimately lead to the blockage of EMT and the invasion of breast cancer cells.

[424]

TÍTULO / TITLE: - The effects of silencing of PI3K p85alpha on 5-FU-induced colorectal cancer cells apoptosis.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):704. doi: 10.1007/s12032-013-0704-7. Epub 2013 Aug 29.

●● Enlace al texto completo (gratuito o de pago) [1007/s12032-013-0704-7](#)

AUTORES / AUTHORS: - Sun Y; Tian H; Wang L; Yang H

INSTITUCIÓN / INSTITUTION: - Gastroenterology Department, The Third Affiliated Hospital of Guangzhou Medical University, Guang Zhou, 510150, China, sunyaniff@163.com.

RESUMEN / SUMMARY: - Colorectal cancer is the third most common malignancy worldwide. 5-fluorouracil (5-FU) is the commonly used chemotherapeutic agent, however, more patients develop resistance. Phosphatidylinositol 3-kinases (PI3Ks) play a crucial role in a wide range of cellular processes associated with malignant behavior including cell growth, migration, and survival. In this study, we show increased expression of PI3K p85alpha during the progression of colorectal cancer. Silencing of PI3K p85alpha in colorectal cancer cells increased disruption of mitochondrial membrane potential and enhanced 5-FU-induced apoptosis. Furthermore, PI3K p85alpha-depletion results in activated expression of apoptosis-associated genes Bcl-6, Bim, and Bax. Our results suggest that knockdown of PI3K p85alpha is a potential therapeutic strategy in the treatment of colorectal cancer.

[425]

TÍTULO / TITLE: - Fluoxetine-induced Apoptosis in Hepatocellular Carcinoma Cells.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3691-7.

AUTORES / AUTHORS: - Mun AR; Lee SJ; Kim GB; Kang HS; Kim JS; Kim SJ

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Toxicology, College of Veterinary Medicine, Chonbuk National University, Jeonju-561-756, Republic of Korea. abbasj@jbnu.ac.kr.

RESUMEN / SUMMARY: - BACKGROUND: In addition to being used to treat mental disorders, a serious complication of cancer, antidepressants have been reported to improve cancer patient immunity, inhibit cell growth and have an antitumor effect on various cancer cell lines. We investigated the apoptotic effect of fluoxetine against the Hep3B human hepatocellular carcinoma cell line. MATERIALS AND METHODS: After treatments of Hep3B cells with fluoxetine, we measured cell viability, reactive oxygen species (ROS), mitochondrial membrane potential (MMP) and activation of mitogen-activated protein kinases (MAPK). RESULTS: Fluoxetine reduced the viability of cancer

cells, induced loss of MMP and formation of ROS, reduced expression of extracellular signal-regulated kinase ½ and increased expression of c-JUN N-terminal kinase and p38 MAPK. N-Acetylcysteine, an oxidant-scavenger, and 1,2-bis (o-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid (BAPTA-AM), an intracellular Ca(2+) chelator, prevented fluoxetine-induced modulation of MAPK. CONCLUSION: Fluoxetine appears to exhibit an apoptotic effect against Hep3B cells through the loss of MMP, formation of ROS and modulation of MAPK activities.

[426]

TÍTULO / TITLE: - MK-2206, an AKT Inhibitor, Promotes Caspase-Independent Cell Death and Inhibits Leiomyoma Growth.

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

REVISTA / JOURNAL: - Endocrinology. 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1210/en.2013-1389](#)

AUTORES / AUTHORS: - Sefton EC; Qiang W; Serna V; Kurita T; Wei JJ; Chakravarti D; Kim JJ

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology (E.C.S., W.Q., V.S., T.K., D.C., J.J.K.), Division of Reproductive Biology Research, and Department of Pathology (J.-J.W.), Northwestern University Feinberg School of Medicine, Chicago, Illinois, 60611.

RESUMEN / SUMMARY: - Uterine leiomyomas (ULs), benign tumors of the myometrium, are the number one indication for hysterectomies in the United States due to a lack of an effective alternative therapy. ULs show activation of the pro-survival AKT pathway compared with normal myometrium; however, substantial data directly linking AKT to UL cell survival are lacking. We hypothesized that AKT promotes UL cell survival and that it is a viable target for inhibiting UL growth. We used the investigational AKT inhibitor MK-2206, currently in phase II trials, on cultured primary human UL and myometrial cells, immortalized leiomyoma cells, and in leiomyoma grafts grown under the kidney capsule in mice. MK-2206 inhibited AKT and PRAS40 phosphorylation but did not regulate serum- and glucocorticoid-induced kinase and ERK1/2, demonstrating its specificity for AKT. MK-2206 reduced UL cell viability and decreased UL tumor volumes. UL cells exhibited disruption of mitochondrial structures and underwent cell death that was independent of caspases. Additionally, mammalian target of rapamycin and p70S6K phosphorylation were reduced, indicating that mammalian target of rapamycin C1 signaling was compromised by AKT inhibition in UL cells. MK-2206 also induced autophagy in UL cells. Pretreatment of primary UL cells with 3-methyladenine enhanced MK-2206-mediated UL cell death, whereas knockdown of ATG5 and/or ATG7 did not significantly influence UL cell viability in the presence of MK-2206. Our data provide molecular evidence for the involvement of AKT in UL cell survival and suggest

that AKT inhibition by MK-2206 may be a viable option to consider for the treatment of ULs.

[427]

TÍTULO / TITLE: - A high Notch pathway activation predicts response to gamma secretase inhibitors in proneural subtype of glioma tumor initiating cells.

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

REVISTA / JOURNAL: - Stem Cells. 2013 Aug 27. doi: 10.1002/stem.1528.

●● Enlace al texto completo (gratis o de pago) [1002/stem.1528](#)

AUTORES / AUTHORS: - Saito N; Fu J; Zheng S; Yao J; Wang S; Liu DD; Yuan Y; Sulman EP; Lang FF; Colman H; Verhaak RG; Yung WK; Koul D

INSTITUCIÓN / INSTITUTION: - Brain Tumor Center, Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

RESUMEN / SUMMARY: - Genomic, transcriptional, and proteomic analyses of brain tumors reveal subtypes that differ in pathway activity, progression, and response to therapy. However, a number of small molecule inhibitors under development vary in strength of subset and pathway-specificity, with molecularly targeted experimental agents tending toward stronger specificity. The Notch signaling pathway is an evolutionarily conserved pathway that plays an important role in multiple cellular and developmental processes. We investigated the effects of Notch pathway inhibition in glioma tumor initiating cell (GIC, hereafter GIC) populations using gamma secretase inhibitors. Drug cytotoxicity testing of 16 GICs showed differential growth responses to the inhibitors, stratifying GICs into responders and non-responders. Responder GICs had an enriched proneural gene signature in comparison to non-responders. Also gene set enrichment analysis revealed 17 genes set representing active Notch signaling components NOTCH1, NOTCH3, HES1, MAML1, DLL-3, JAG2 etc., enriched in responder group. Analysis of TCGA expression data set identified a group (43.9%) of tumors with proneural signature showing high Notch pathway activation suggesting gamma-secretase inhibitors might be of potential value to treat that particular group of proneural GBM. Inhibition of Notch pathway by gamma-secretase inhibitor treatment attenuated proliferation and self-renewal of responder GICs and induces both neuronal and astrocytic differentiation. In vivo evaluation demonstrated prolongation of median survival in an intracranial mouse model. Our results suggest that proneural GBM characterized by high Notch pathway activation may exhibit greater sensitivity to gamma-secretase inhibitor treatment, holding a promise to improve the efficiency of current glioma therapy. Stem Cells 2013.

[428]

TÍTULO / TITLE: - Prediction of Nodal Metastasis and Prognosis of Breast Cancer by ANN-based Assessment of Tumour Size and p53, Ki-67 and Steroid Receptor Expression.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3925-33.

AUTORES / AUTHORS: - Mojarad S; Venturini B; Fulgenzi P; Papaleo R; Brisigotti M; Monti F; Canuti D; Ravaioli A; Woo L; Dlay S; Sherbet GV

INSTITUCIÓN / INSTITUTION: - School of Electrical, Electronic and Computer Engineering, University of Newcastle upon Tyne, Newcastle upon Tyne, England, U.K.

gajanan.sherbet@newcastle.ac.uk.

RESUMEN / SUMMARY: - BACKGROUND: Tumour stage and the appropriate course of treatment in patients with breast cancer are primarily characterized by the state of metastasis in the axillary lymph nodes. In recent years, substantial research has focused on the prediction of lymph node status based on various pathological and molecular markers in order to obviate the necessity to carry out axillary dissection. In the present study, artificial neural network (ANN) is employed as the analysis platform to examine the prognostic significance of a group of well-established prognostic markers for breast cancer outcome prediction in terms of nodal status. Furthermore, we investigated existing interactions between these markers. PATIENTS AND METHODS: The data set contained 66 patient records, where 5 pathological and molecular markers including tumour size, oestrogen receptor status (ER), progesterone receptor status (PR), Ki-67 and p53 expression had been assessed for each patient. The spread of metastasis to the axillary lymph nodes was clinically diagnosed and patients were accordingly categorized into node-positive and node-negative groups. The aforementioned markers were analyzed using a probabilistic neural network (PNN) for nodal status prediction which was considered as the network output. Furthermore, the interactions between these markers were evaluated using different marker combinations as the network input for finding the best marker arrangement for nodal prediction. RESULTS: The best prediction accuracy was obtained by a 3-marker combination including tumour size, PR and p53 with 71% accuracy for nodal prediction. Leaving out ER and PR from the full marker set showed approximately the same variations in the results, which is an indication of the direct correlation of these two markers. Furthermore, tumour size was proved to be the most significant individual marker for predicting nodal metastasis. However, when used in combination with Ki-67 the prediction results drop significantly. CONCLUSION: The results presented here indicate that molecular and pathological markers can provide useful information for early-stage prognosis. However, the interactions between these markers must be considered in order to achieve accurate and reliable prediction.

TÍTULO / TITLE: - The monoclonal antibody CH12 augments 5-fluorouracil-induced growth suppression of hepatocellular carcinoma xenografts expressing epidermal growth factor receptor variant III.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Sep 2. pii: S0304-3835(13)00623-X. doi: 10.1016/j.canlet.2013.08.038.

●● Enlace al texto completo (gratis o de pago) 1016/j.canlet.2013.08.038

AUTORES / AUTHORS: - Jiang H; Dong Q; Luo X; Shi B; Wang H; Gao H; Kong J; Zhang J; Li Z

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncogenes & Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, China.

RESUMEN / SUMMARY: - 5-Fluorouracil (5-FU) is one of the most common chemotherapeutic agents used for the treatment of hepatocellular carcinoma (HCC). However, chemoresistance has precluded the use of 5-FU alone in clinical regimens. Combination therapies with 5-FU and other anticancer agents are considered to be a therapeutic option for patients with HCC. We previously reported that the expression of epidermal growth factor receptor variant III (EGFRvIII) can decrease the sensitivity of HCC cells to 5-FU. To overcome this problem, in this study, we elucidated the mechanism underlying EGFRvIII-mediated 5-FU resistance. We observed that EGFRvIII expression can induce miR-520d-3p downregulation and the ensuing upregulation of the transcription factor E2F-1 and the enzyme thymidylate synthase (TS), which may lead to drug resistance. Intriguingly, we found that CH12, a monoclonal antibody directed against EGFRvIII, and 5-FU together had an additive antitumor effect on EGFRvIII-positive HCC xenografts and significantly improved survival in all mice with established tumors when compared with either 5-FU or CH12 alone. Mechanistically, compared with 5-FU alone, the combination more noticeably downregulated EGFR phosphorylation and Akt phosphorylation as well as the expression of the apoptotic protector Bcl-xL and the cell cycle regulator cyclin D1. Additionally, the combination upregulated the expression of the cell cycle inhibitor p27 in in vivo treatment. More interestingly, CH12 treatment upregulated miR-520-3p and downregulated E2F-1 and TS at the mRNA and protein levels. Collectively, these observations suggest that the combination of 5-FU with mAb CH12 is a potential means of circumventing EGFRvIII-mediated 5-FU resistance in HCC.

[430]

TÍTULO / TITLE: - PPARgamma mediates the effects of WIN55,212-2, an synthetic cannabinoid, on the proliferation and apoptosis of the BEL-7402 hepatocarcinoma cells.

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

REVISTA / JOURNAL: - Mol Biol Rep. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1007/s11033-013-2741-x](https://doi.org/10.1007/s11033-013-2741-x)

AUTORES / AUTHORS: - Hong Y; Zhou Y; Wang Y; Xiao S; Liao DJ; Zhao Q

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Guangzhou Medical University, Guangzhou, 510182, China.

RESUMEN / SUMMARY: - Cannabis sativa has long been used as a traditional medicine in China. Among its effective compounds are cannabinoids. This study determined the effect of WIN55,212-2 (WIN), a synthetic cannabinoid, on the BEL-7402 human hepatocellular carcinoma (HCC) cell line. The results showed that WIN could decrease the proliferation of BEL-7402 cells. Moreover, WIN could cause apoptosis of the cells via up-regulation of Bax expression, down-regulation of Bcl-2 expression, induction of the mitochondrial membrane potential, increase of caspase-3, -8 and -9 activities, and induction of the cleavage of caspase-3 and poly-ADP-ribose polymerase (PARP). The WIN-induced apoptosis was accompanied by the up-regulation of PPARgamma expression, the activation of PPARgamma DNA binding activity, and a down-regulation of PPARgamma target oncogene c-myc. Conversely, the effects of WIN could be attenuated by PPARgamma antagonist GW9662, and the WIN induced PPARgamma expression was partially attenuated by AM630, a cannabinoid receptor-2 antagonist, whereas the WIN-induced reduction of c-myc expression was partially restored by GW9662. Collectively, our results suggest that WIN can decrease the proliferation and cause apoptosis of the BEL-7402 cells via a mitochondrial-caspase pathway and mediated by PPARgamma. These results may provide a basis for the application of WIN in HCC treatment.

[431]

TÍTULO / TITLE: - United States Food and Drug Administration approved oral kinase inhibitors for the treatment of malignancies.

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

REVISTA / JOURNAL: - Curr Probl Cancer. 2013 May-Jun;37(3):110-44. doi: 10.1016/j.crrprobcancer.2013.06.001.

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

[1016/j.crrprobcancer.2013.06.001](https://doi.org/10.1016/j.crrprobcancer.2013.06.001)

AUTORES / AUTHORS: - Jeong W; Doroshow JH; Kummar S

[432]

TÍTULO / TITLE: - Crizotinib overcomes hepatocyte growth factor-mediated resistance to gefitinib in EGFR-mutant non-small-cell lung cancer cells.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Nov;24(10):1039-46. doi: 10.1097/CAD.000000000000011.

- Enlace al texto completo (gratis o de pago)

[1097/CAD.0000000000000011](#)

AUTORES / AUTHORS: - Chen X; Zhou JY; Zhao J; Chen JJ; Ma SN; Zhou JY

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, Thoracic Disease Diagnosis and Treatment Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

RESUMEN / SUMMARY: - Acquired resistance develops ultimately in most non-small-cell lung cancer patients with epidermal growth factor receptor (EGFR) mutations who initially respond to EGFR tyrosine kinase inhibitors. Overexpression of hepatocyte growth factor (HGF) contributes to a considerable part of acquired resistance. Therefore, novel approaches are required for better management to overcome the resistance. Here, we tested whether crizotinib (PF02341066), a MET kinase inhibitor, can overcome two different HGF-triggered mechanisms of resistance to gefitinib in human EGFR mutant lung cancer cell lines HCC827 and PC-9. Compared with the monotherapy, the combined treatment of crizotinib and gefitinib induced apoptosis and significantly inhibited the growth of cells in the presence of HGF by blocking the MET/PI3K/Akt pathway. Further, we demonstrated that crizotinib plus gefitinib successfully prevented the emergence of gefitinib-resistant HCC827 cells induced by transient exposure to HGF. In vivo, the combination therapy with crizotinib and gefitinib also markedly suppressed the growth of gefitinib-resistant mouse xenografts established by injecting HCC827 cells mixed with HGF-producing fibroblasts (MRC-5 cells) subcutaneously into severe combined immunodeficient mice. In conclusion, these findings provided preclinical evidence that crizotinib can be used in the treatment of HGF-induced resistance to gefitinib in EGFR mutant lung cancer.

[433]

TÍTULO / TITLE: - Hypoxia-regulated gene expression and prognosis in loco-regional gastroesophageal cancer.

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

REVISTA / JOURNAL: - Acta Oncol. 2013 Oct;52(7):1327-35. doi: 10.3109/0284186X.2013.818247. Epub 2013 Aug 19.

- Enlace al texto completo (gratis o de pago) [3109/0284186X.2013.818247](#)

AUTORES / AUTHORS: - Winther M; Alsner J; Tramm T; Nordmark M

INSTITUCIÓN / INSTITUTION: - Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

RESUMEN / SUMMARY: - Abstract Gastroesophageal cancers are heterogeneous diseases with a poor outcome. Prognostic and predictive factors are needed to improve patient survival. Hypoxia is an adverse prognostic factor and is associated with resistance to chemo- and radiotherapy in various cancers. However, knowledge on the impact of hypoxia in gastroesophageal cancer is limited. The aim of this study was to evaluate

potential prognostic factors in terms of a subset of hypoxia-responsive genes and clinicopathological parameters in patients with gastroesophageal cancer. Material and methods. Ninety-five patients with loco-regional gastroesophageal cancer treated with curative intent were retrospectively analyzed. Based on formalin-fixed paraffin-embedded diagnostic biopsies gene expressions of 15 hypoxia-induced and pH-independent genes from a previously described hypoxia gene expression classifier was quantified. The prognostic impact was evaluated for overall survival (OS) and disease-specific survival (DSS). Uni- and multivariate Cox proportional hazards model was used to identify hypoxia-responsive gene expression and clinicopathological parameters as prognostic markers. Results. An unsupervised hierarchical clustering of hypoxia regulated genes showed two well-differentiated patient clusters: One cluster of tumors with high gene expression and another with low gene expression, indicating a more hypoxic genotype versus a less hypoxic genotype respectively. As the group of esophageal squamous cell carcinomas (ESCC) alone showed intra-group heterogeneity this group was ranked according to the gene expression of the 15 genes. The most hypoxic third showed a trend towards a poorer outcome in terms of OS [HR = 0.48 (CI 0.21-1.07), p = 0.07] and DSS [HR = 0.48 (CI 0.18-1.24), p = 0.13]. Treatment response was identified as an independent prognostic factor for DSS in the group of ESCC [HR = 0.21 (CI 0.05-0.95), p = 0.04]. Conclusion. Gene expression analysis of 15 hypoxia-responsive genes was identified as a promising prognostic marker in patients with ESCC. Further studies confirming these results in larger patient cohorts are needed.

[434]

TÍTULO / TITLE: - Effects of SAHA on proliferation and apoptosis of hepatocellular carcinoma cells and hepatitis B virus replication.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Aug 21;19(31):5159-64. doi: 10.3748/wjg.v19.i31.5159.

●● [Enlace al texto completo \(gratis o de pago\) 3748/wjg.v19.i31.5159](#)

AUTORES / AUTHORS: - Wang YC; Yang X; Xing LH; Kong WZ

INSTITUCIÓN / INSTITUTION: - Ying-Chun Wang, Xu Yang, Lan-Hua Xing, Wei-Zong Kong, Department of Gastroenterology, Affiliated Zhongshan Hospital of Dalian University, Dalian 116001, Liaoning Province, China.

RESUMEN / SUMMARY: - AIM: To investigate the effects of suberoylanilide hydroxamic acid (SAHA) on proliferation and apoptosis of a human hepatocellular carcinoma cell line (HepG2.2.15) and hepatitis B virus (HBV) replication. METHODS: HepG2.2.15 cells were treated with different concentrations of SAHA. Cell morphology was examined by confocal laser scanning microscopy, and cell proliferation was determined using a MTT colorimetric assay. Flow cytometry was used to detect apoptosis and determine cell cycle phase, while hepatitis B surface antigen and hepatitis B e antigen content

were measured using chemiluminescence. Reverse transcription polymerase chain reaction was performed to measure HBV DNA in cell lysate. RESULTS: Cell proliferation rates were significantly reduced by the addition of SAHA. The inhibitory effect of SAHA on cell proliferation was both time- and dose-dependent. After 24 h of treatment with SAHA, the early cell apoptotic rate increased from 3.25% to 21.02% (P = 0.041). The proportion of G0/G1 phase cells increased from 50.3% to 65.3% (P = 0.039), while that of S phase cells decreased from 34.9% to 20.6% (P = 0.049). After 48 h of treatment, hepatitis B surface antigen and hepatitis B e antigen content increased from 12.33 +/- 0.62 to 25.42 +/- 2.67 (P = 0.020) and 28.92 +/- 1.24 to 50.48 +/- 1.85 (P = 0.026), respectively. Furthermore, HBV DNA content increased from 4.54 +/- 0.46 to 8.34 +/- 0.59 (P = 0.029). CONCLUSION: SAHA inhibits HepG2.2.15 cell proliferation, promotes apoptosis, and stimulates HBV replication. In combination with anti-HBV drugs, SAHA may potentially be used cautiously for treatment of hepatocellular carcinoma.

[435]

TÍTULO / TITLE: - Decreased expression of interleukin-36alpha correlates with poor prognosis in hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Cancer Immunol Immunother. 2013 Sep 6.

●● Enlace al texto completo (gratis o de pago) [1007/s00262-013-1471-1](#)

AUTORES / AUTHORS: - Pan QZ; Pan K; Zhao JJ; Chen JG; Li JJ; Lv L; Wang DD; Zheng HX; Jiang SS; Zhang XF; Xia JC

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China, Department of Biotherapy, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, 510060, People's Republic of China.

RESUMEN / SUMMARY: - Interleukin-36alpha (IL-36alpha) has been found to have a prominent role in the pathogenesis of inflammatory disorders; however, little is known about the role of IL-36alpha in cancer. In this study, we investigated the expression, prognostic value, and the underlying antitumor mechanism of IL-36alpha in hepatocellular carcinoma (HCC). From immunohistochemistry analysis, IL-36alpha expression was lower in poorly differentiated HCC cells. In clinicopathological analysis, low IL-36alpha expression significantly correlated with tumor size, histological differentiation, tumor stage, and vascular invasion, and low intratumoral IL-36alpha expression had significantly worse overall survival rates and shorter disease-free survival rates. Moreover, intratumoral IL-36alpha expression was an independent risk factor for overall survival. Consecutive sections were used to detect CD3+, CD8+, and CD4+ tumor-infiltrating lymphocytes (TILs), and we found that high-IL-36alpha-expressing tumor tissues exhibited a significantly higher proportion of intratumoral CD3+ and CD8+ TILs, but not CD4+ TILs. Our in vitro model confirmed that supernatant from IL-36alpha-overexpressing human HCC cells had an increased capacity to recruit

CD3+ and CD8+ T cells. Consistently, mouse HCC cells engineered to overexpress IL-36alpha demonstrated markedly delayed growth in vivo, as well as higher levels of intratumoral CD3+ and CD8+ TILs, compared with control mice. In vitro chemotaxis analysis also showed that mouse HCC cells overexpressing IL-36alpha could recruit more number of CD3+ and CD8+ T cells. These results show that IL-36alpha expression may play a pivotal role in determining the prognosis of patients with HCC, which we attribute to the activation of adaptive T cell immunity, especially CD8+ T cell immune response.

[436]

TÍTULO / TITLE: - Prognostic implication of the CpG island methylator phenotype in colorectal cancers depends on tumour location.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 20;109(4):1004-12. doi: 10.1038/bjc.2013.430. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.430](#)

AUTORES / AUTHORS: - Bae JM; Kim JH; Cho NY; Kim TY; Kang GH

INSTITUCIÓN / INSTITUTION: - 1] Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea [2] Laboratory of Epigenetics, Cancer Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea.

RESUMEN / SUMMARY: - Background:Colorectal cancer (CRC) is usually categorised as proximal or distal CRC. Recently, many researchers have tried to determine the molecular heterogeneity of CRCs along bowel subsites. However, the differential effects of the CpG island methylator phenotype (CIMP) and microsatellite instability (MSI) on the clinical outcome according to tumour location are not well-known.Methods:We analysed clinicopathologic and molecular characteristics, including CIMP, MSI, KRAS and BRAF mutations, in 734 CRCs according to bowel subsites. And the prognostic value of CIMP and MSI was analysed according to tumour location.Results:We found a linear increase of female predominance, T, N category, stage, differentiation, absence of luminal necrosis, tumour -infiltrating lymphocytes, Crohn's-like lymphoid reaction, serration and mucin production from the rectum to caecum. CpG island methylator phenotype -high and MSI-high gradually increased from the rectum to caecum. CpG island methylator phenotype is a poor prognostic factor of overall survival (hazard ratio (HR): 4.13, 95% confidence interval (CI): 1.27-13.46) and disease-free survival (HR: 2.90, 95% CI: 1.04-8.08) in rectal cancers.Conclusion:Clinicopathologic and molecular profiles of CRCs gradually change along bowel subsites, and the prognostic implication of CIMP is different according to tumour location.

[437]

TÍTULO / TITLE: - Senescence-associated protein p400 is a prognostic marker in renal cell carcinoma.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2245-53. doi: 10.3892/or.2013.2698. Epub 2013 Aug 26.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2698](#)

AUTORES / AUTHORS: - Macher-Goeppinger S; Bermejo JL; Schirmacher P; Pahernik S; Hohenfellner M; Roth W

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, University Hospital of Heidelberg, D-69120 Heidelberg, Germany.

RESUMEN / SUMMARY: - Mutations of the von Hippel-Lindau (VHL) tumor suppressor gene cause hereditary and sporadic renal cell carcinomas (RCCs). The best characterized function of VHL protein is suppression of the alpha subunit of hypoxia inducible factor (HIF). Additional VHL functions have been reported, including induction of senescence upon loss of VHL mediated by downregulation of the chromatin remodeling factor p400. Induction of senescence either by oncogene activation or inactivation of tumor suppressors is considered a critical feature of mammalian cells by which to suppress tumorigenesis. In the present study, we investigated the relationship between the expression of p400 and patient survival following RCC diagnosis taking advantage of a large and well-documented series of RCC patients with long-term follow-up information. The expression of p400 was measured by immunohistochemistry using a tissue microarray containing tumor tissue samples from 868 RCC patients. Chi-squared tests, Kaplan-Meier curves, Cox regression models and Spearman's rank correlation estimates were used to investigate the possible relationship between p400 expression and Ki-67 proliferative index, clinical and pathological characteristics and patient survival. Complete loss of p400 expression was detected in 64% of all tumor specimens, and decreased p400 expression was associated with advanced tumor stage, higher grade of malignancy and regional lymph node metastasis. Among well-differentiated RCCs, high proliferation (Ki-67 index >10) was found in 12% of carcinomas with an increased p400 expression, compared to 5% of RCCs with decreased p400 expression. Multiple Cox regression indicated that patients with low proliferative tumors and increased p400 expression had a 60% lower cancer-specific mortality risk compared to those affected by low proliferative RCCs with decreased p400 expression. In summary, patients affected by highly proliferative tumors with decreased p400 expression exhibit a poor prognosis by multiple Cox regression. Our data suggest that the highly proliferative, decreased-p400 subgroup of RCCs represents tumors that are characterized by a loss of the tumor-suppressive mechanism of senescence.

[438]

TÍTULO / TITLE: - TNF-like weak inducer of apoptosis (TWEAK) promotes glioblastoma cell chemotaxis via Lyn activation.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt289](#)

AUTORES / AUTHORS: - Dhruv HD; Whitsett TG; Jameson NM; Patel F; Winkles JA; Berens ME; Tran NL

INSTITUCIÓN / INSTITUTION: - Cancer and Cell Biology Division, The Translational Genomics Research Institute (TGen), Phoenix, AZ.

RESUMEN / SUMMARY: - The long-term survival of patients with glioblastoma (GB) is compromised by the proclivity for local invasion into the surrounding normal brain, escaping surgical resection and contributing to therapeutic resistance. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK), a member of the tumor necrosis factor superfamily, can stimulate glioma cell invasion via binding to fibroblast growth factor-inducible 14 (Fn14) and subsequent activation of the Rho GTPase family member Rac1. Here, we demonstrate that TWEAK acts as a chemotactic factor for glioma cells, a potential process for driving cell invasion into the surrounding brain tissue. TWEAK exposure induced the activation of Src-family kinases (SFK), and pharmacologic suppression of SFK activity inhibited TWEAK-induced chemotactic migration. We employed a multiplexed Luminex assay and identified Lyn as a candidate SFK activated by TWEAK. Depletion of Lyn suppressed TWEAK-induced chemotaxis and Rac1 activity. Furthermore, Lyn gene expression levels increase with primary glioma tumor grade and inversely correlate with patient survival. These results show that TWEAK-induced glioma cell chemotaxis is dependent upon Lyn kinase function, and thus, provides opportunities for therapeutic targeting of this deadly disease.

[439]

TÍTULO / TITLE: - Involvement of autophagy in recombinant human arginase-induced cell apoptosis and growth inhibition of malignant melanoma cells.

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

REVISTA / JOURNAL: - Appl Microbiol Biotechnol. 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1007/s00253-013-5118-0](#)

AUTORES / AUTHORS: - Wang Z; Shi X; Li Y; Zeng X; Fan J; Sun Y; Xian Z; Zhang G; Wang S; Hu H; Ju D

INSTITUCIÓN / INSTITUTION: - Department of Biosynthesis, School of Pharmacy, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - Recombinant human arginase (rhArg) has been developed for arginine derivation therapy of cancer and is currently in clinical trials for a variety of

malignant solid tumors. In this study, we reported for the first time that rhArg could induce obvious autophagy in human melanoma cells; inhibition of autophagy by chloroquine (CQ) significantly increased rhArg-induced cell apoptosis and growth inhibition of A375 cells. A significant increase in mitochondrial membrane potential loss and elevated intracellular reactive oxygen species (ROS) levels were detected in A375 cells after rhArg treatment when compared with control. Membrane transition inhibitor cyclosporine A blocked autophagy and accelerated cell death induced by rhArg, indicating that rhArg induced autophagy via mitochondria pathway. Furthermore, antioxidant N-acetyl-L-cysteine suppressed rhArg-induced autophagy and rescued cells from cell growth inhibition, suggesting that ROS played an important role in rhArg-induced A375 cell growth inhibition and autophagy. Akt/mTOR signaling pathway was involved in autophagy induced by rhArg in a time-dependent manner. Moreover, rhArg could induce ERK1/2 activation in a dose- and time-dependent manner and rhArg-induced autophagy was attenuated when p-ERK1/2 was inhibited by MEK ½ inhibitor, U0126. Taken together, this study provides new insight into the molecular mechanism of autophagy involved in rhArg-induced cell apoptosis and growth inhibition, which facilitates the development of rhArg in combination with CQ as a potential therapy for malignant melanoma.

[440]

TÍTULO / TITLE: - Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Aug;141(1):119-23. doi: 10.1007/s10549-013-2675-y. Epub 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2675-y](#)

AUTORES / AUTHORS: - Di Lauro L; Vici P; Del Medico P; Laudadio L; Tomao S; Giannarelli D; Pizzuti L; Sergi D; Barba M; Maugeri-Sacca M

INSTITUCIÓN / INSTITUTION: - Division of Medical Oncology B, "Regina Elena" National Cancer Institute, Via Elio Chianesi 53, 00154, Rome, Italy.

RESUMEN / SUMMARY: - The role of aromatase inhibitors combined with gonadotropin-releasing hormone analog in metastatic male breast cancer patients remains unknown. In this retrospective study we evaluated the activity of letrozole combined with a gonadotropin-releasing hormone analog as a first- or second-line therapy for metastatic male breast cancer patients. 19 men entered the study. We did not observe any grade 3 or 4 adverse events. 2 patients (10.5 %) had complete response, 7 patients (36.8 %) experienced a partial response, 7 patients (36.8 %) had stable disease lasting ≥ 6 months, and 3 patients (15.8 %) had progressive disease. Overall, the disease control rate was 84.2 %. Median progression-free survival was 12.5 months (95 % CI 8.2-16.9), median overall survival was 35.8 months (95 % CI 24.4-49.2), 1- and 2-year

survival rates were 89.5 and 67 %, respectively. Interestingly, 3 out of 4 patients treated with the combination following disease progression while on aromatase inhibitor monotherapy confirmed or improved the best overall response observed in the first-line setting. The combination of letrozole and gonadotropin-releasing hormone analog is effective and safe in hormone-receptor positive, metastatic male breast cancer patients.

[441]

TÍTULO / TITLE: - Transferrin-conjugated magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel for brain glioma treatment.

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

REVISTA / JOURNAL: - Biomaterials. 2013 Nov;34(33):8511-20. doi: 10.1016/j.biomaterials.2013.07.075. Epub 2013 Aug 6.

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

[1016/j.biomaterials.2013.07.075](https://doi.org/10.1016/j.biomaterials.2013.07.075)

AUTORES / AUTHORS: - Cui Y; Xu Q; Chow PK; Wang D; Wang CH

INSTITUCIÓN / INSTITUTION: - School of Materials Science and Engineering, Tongji University, 4800 Caoan Road, Shanghai 201804, PR China; Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576, Singapore.

RESUMEN / SUMMARY: - The effective treatment of malignant brain glioma is hindered by the poor transport across the blood-brain barrier (BBB) and the low penetration across the blood-tumor barrier (BTB). In this study, transferrin-conjugated magnetic silica PLGA nanoparticles (MNP-MSN-PLGA-Tf NPs) were formulated to overcome these barriers. These NPs were loaded with doxorubicin (DOX) and paclitaxel (PTX), and their anti-proliferative effect was evaluated in vitro and in vivo. The in vitro cytotoxicity of drug-loaded NPs was evaluated in U-87 cells. The delivery and the subsequent cellular uptake of drug-loaded NPs could be enhanced by the presence of magnetic field and the usage of Tf as targeting ligand, respectively. In particular, cells treated with DOX-PTX-NPs-Tf with magnetic field showed the highest cytotoxicity as compared to those treated with DOX-PTX-NPs-Tf, DOX-PTX-NPs, DOX-PTX-NPs-Tf with free Tf. The in vivo therapeutic efficacy of drug-loaded NPs was evaluated in intracranial U-87 MG-luc2 xenograft of BALB/c nude mice. In particular, the DOX-PTX-NPs-Tf treatment exhibited the strongest anti-glioma activity as compared to the PTX-NPs-Tf, DOX-NPs-Tf or DOX-PTX-NPs treatment. Mice did not show acute toxicity after administrating with blank MNP-MSN-PLGA-Tf NPs. Overall, MNP-MSN-PLGA-Tf NPs are promising carriers for the delivery of dual drugs for effective treatment of brain glioma.

[442]

TÍTULO / TITLE: - PHII-7 inhibits cell growth and induces apoptosis in leukemia cell line K562 as well as its MDR- counterpart K562/A02 through producing reactive oxygen species.

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

REVISTA / JOURNAL: - Eur J Pharmacol. 2013 Jul 30. pii: S0014-2999(13)00560-8. doi: 10.1016/j.ejphar.2013.07.038.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejphar.2013.07.038

AUTORES / AUTHORS: - Peng H; Yuan X; Shi R; Wei X; Ren S; Yan C; Ding Y; Lin Y; Fan D; Yang M; Zhang Y; Xiong D

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Experimental Hematology, Institute of Hematology & Hospital of Blood Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, PR China; Department of Pharmacy, First affiliated Hospital of Nanchang University, Nanchang, Jiangxi, PR China.

RESUMEN / SUMMARY: - Multidrug resistance (MDR) is a major obstacle that hinders the efficacy of chemotherapy in many human malignancies. PHII-7 is a derivative of indirubin, which was designed and synthesized by our laboratory. Our preliminary work indicated its potent antitumor activities in vitro and in vivo. Furthermore, based on the model of MDR cell line, we found its powerful effects in inhibiting the expression of P-glycoprotein (P-gp) and killing multidrug-resistant (MDR) cells with the detailed mechanism remained to be explored. Reactive oxygen species are known for high reactive activity as they possess unmatched electrons. In this study, we showed that PHII-7 generated equal reactive oxygen species in parental K562 and its counterpart MDR K562/A02 cells. Pre-incubation with thiol antioxidants glutathione or N-acetyl-cysteine(NAC) almost abolished the cytotoxicity of PHII-7. Moreover, NAC abrogated DNA damage, cell cycle arrests and apoptosis induced by PHII-7. Our results collectively indicated that reactive oxygen species production induced by PHII-7 contributed to both apoptosis and cell cycle arrests in MDR K562/A02 cells, thus extending our prior related findings. Notably, JNK phosphorylation was also induced by PHII-7 and pre-incubated of K562/A02 cells with NAC or inhibitor of JNK(SP006125) eliminated P-gp downregulation. Taken together, our results may provide a detailed biochemical basis for further clinical application of PHII-7.

[443]

TÍTULO / TITLE: - ICP: A novel approach to predict prognosis of prostate cancer with inner-class clustering of gene expression data.

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

REVISTA / JOURNAL: - Comput Biol Med. 2013 Oct 1;43(10):1363-73. doi: 10.1016/j.compbiomed.2013.06.014. Epub 2013 Jul 4.

- Enlace al texto completo (gratis o de pago)

1016/j.combiomed.2013.06.014

AUTORES / AUTHORS: - Kim H; Ahn J; Park C; Yoon Y; Park S

INSTITUCIÓN / INSTITUTION: - Department of Computer Science, Yonsei University, South Korea.

RESUMEN / SUMMARY: - Prostate cancer has heterogeneous characteristics. For that reason, even if tumors appear histologically similar to each other, there are many cases in which they are actually different, based on their gene expression levels. A single tumor may have multiple expression levels with both high-risk cancer genes and low-risk cancer genes. We can produce more useful models for stratifying prostate cancers into high-risk cancer and low-risk cancer categories by considering the range in each class through inner-class clustering. In this paper, we attempt to classify cancers into high-risk (aggressive) prostate cancer and low-risk (non-aggressive) prostate cancer using ICP (Inner-class Clustering and Prediction). Our model classified more efficiently than the models of the algorithms used for comparison. After discovering a number of genes linked to prostate cancer from the gene pairs used in our classification, we discovered that the proposed method can be used to find new unknown genes and gene pairs which distinguish between high-risk cancer and low-risk cancer.

[444]

TÍTULO / TITLE: - PROTEOME PROFILING OF CANCER-ASSOCIATED FIBROBLASTS IDENTIFIES NOVEL PRO-INFLAMMATORY SIGNATURES AND PROGNOSTIC MARKERS FOR COLORECTAL CANCER.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 11.

- Enlace al texto completo (gratis o de pago) 1158/1078-0432.CCR-13-1130

AUTORES / AUTHORS: - Torres S; Bartolome RA; Mendes M; Barderas R; Fernandez-Acenero MJ; Pelaez-Garcia A; Pena C; Lopez-Lucendo M; Villar-Vazquez R; Garcia de Herreros A; Bonilla F; Casal I

INSTITUCIÓN / INSTITUTION: - Functional Proteomics. Department of Cellular and Molecular Medicine, Centro de Investigaciones Biologicas.

RESUMEN / SUMMARY: - PURPOSE: Cancer-associated fibroblasts (CAFs) are essential components of the stroma that play a critical role in cancer progression. This study aimed to identify novel CAFs markers that might contribute to the invasion and the prognosis of colorectal cancer. EXPERIMENTAL DESIGN: The azoxymethane/dextran sodium sulfate mouse model of sporadic colon cancer represents an adequate source for the isolation of CAFs and normal fibroblasts (NFs). By using the explants technique we purified CAFs and NFs from colon tissues. Whole cell extracts and supernatants were subjected to in-depth quantitative proteomic analysis by tandem mass

spectrometry. Further validations of up-regulated proteins in CAFs were carried out by chemokine microarray analysis and immunohistochemistry of mouse and human tissues. RESULTS: Using a fold-change ≥ 1.4 , we found 132 and 125 differentially-expressed proteins in whole cell extracts and supernatants, respectively. We found CAFs-associated pro-inflammatory and desmoplastic signatures. The pro-inflammatory signature was composed of several cytokines. Among them, CCL2 and CCL8 caused an increase in migration and invasion of colorectal cancer KM12 cells. The desmoplastic signature was composed of 30 secreted proteins. In mouse and human samples, expression of LTBP2, CDH11, OLFML3 and, particularly, FSTL1 was significantly increased in the tumoral stroma, without significant expression in the cancer epithelial cells. The combination of CALU and CDH11 stromal expression showed a significant association to disease-free survival and poor prognosis. CONCLUSIONS: We have identified LTBP2, CDH11, OLFML3 and FSTL1 as selective biomarkers of cancer stroma and CALU and CDH11 as candidate stromal biomarkers of prognostic significance in colon cancer.

[445]

TÍTULO / TITLE: - FUNCTIONAL HETEROGENEITY OF CANCER-ASSOCIATED FIBROBLASTS FROM HUMAN COLON TUMORS SHOWS SPECIFIC PROGNOSTIC GENE EXPRESSION SIGNATURE.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0694](#)

AUTORES / AUTHORS: - Herrera M; Islam AB; Herrera A; Martin P; Garcia V; Silva J; Garcia JM; Salas C; Casal I; Garcia de Herreros A; Bonilla F; Pena C

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Hospital Universitario Puerta de Hierro, Majadahonda.

RESUMEN / SUMMARY: - PURPOSE: Cancer-associated fibroblasts (CAFs) actively participate in reciprocal communication with tumor cells and with other cell types in the microenvironment, contributing to a tumor-permissive neighborhood and promoting tumor progression. The aim of this study is the characterization of how CAFs from primary human colon tumors promote migration of colon cancer cells. EXPERIMENTAL DESIGN: Primary CAF cultures from 15 primary human colon tumors were established. Their enrichment in CAFs was evaluated by the expression of various epithelial and myofibroblast specific markers. Co-culture assays of primary CAFs with different colon tumor cells were performed to evaluate pro-migratory CAF-derived effects on cancer cells. Gene expression profiles were developed to further investigate CAF characteristics. RESULTS: Co-culture assays showed significant differences in fibroblast-derived paracrine pro-migratory effects on cancer cells. Moreover, association between CAFs' pro-migratory effects on cancer cells and classical fibroblast

activation or stemness markers was observed. CAF gene expression profiles were analyzed by microarray to identify deregulated genes in different pro-migratory CAFs. The gene expression signature, derived from the most pro-tumorigenic CAFs, was identified. Interestingly, this “CAF signature” showed a remarkable prognostic value for the clinical outcome of colon cancer patients. Moreover, this prognostic value was validated in an independent series of 142 colon cancer patients, by RT-qPCR, with a set of four genes included in the “CAF signature”. CONCLUSIONS: In summary, these studies demonstrate for the first time the heterogeneity of primary CAFs’ effect on colon cancer cell migration. A CAF gene expression signature able to classify colon cancer patients into high- and low-risk groups was identified.

[446]

TÍTULO / TITLE: - Overexpression of Bcl2 protein predicts chemoresistance in acute myeloid leukemia: Its correlation with FLT3.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(6):666-75. doi: 10.4149/neo_2013_085.

●● [Enlace al texto completo \(gratis o de pago\) 4149/neo_2013_085](#)

AUTORES / AUTHORS: - Mehta SV; Shukla SN; Vora HH

RESUMEN / SUMMARY: - Potential prognostic biomarkers in acute myeloid leukemia (AML) can be identified by understanding the cellular pathway and molecular changes underlying leukemogenesis. Deregulation of apoptosis is one of the important features of AML and to understand the molecular mechanism underlying apoptosis and its contribution to tumor progression, this study aimed to evaluate anti-apoptotic Bcl2 protein expression in AML and correlate with FLT3 parameters for their role in prognosis of disease. Bcl2 and FLT3 protein expression was quantified by flow cytometry on leukemic blasts in total 174 de novo AML, myelodysplastic syndrome (MDS) and aplastic anemia patients. FLT3 internal tandem duplication (ITD), Tyrosine kinase domain (TKD) point mutations and quantification of mRNA level was carried out using PCR and RT-PCR methods. The incidence of Bcl2 positivity was 71% in AML patients. Bcl2 positivity was significantly associated with CD34+ and CD117+ AML. Bcl2 positivity tended to be associated with reduced DFS while Bcl2 positivity with FLT3 protein positivity was significantly associated with reduced DFS. In multivariate analysis, Bcl2+ and combined Bcl2+/FLT3 protein+ along with high WBC count emerged as poor prognostic factors for reduced DFS and high blast count for predicting reduced OS. In MDS patients, the incidence of Bcl2 expression was high while in aplastic anemia patients, incidence of Bcl2 expression was low. Patients with Bcl2 and FLT3 protein positivity showed significantly reduced DFS suggesting parallel role of these proteins in imparting chemoresistance to the leukemic cells. Keywords: Bcl2, FLT3, AML, MDS, aplastic anemia, flow cytometry, PCR, RTPCR.

[447]

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. 2013 Sep 20. doi: 10.4149/neo_2014_012.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2014_012](#)

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 an unfavorable independent poor prognostic parameter for hepatocellular carcinoma. Keywords: SGTB; Heat stress cognate 70 (Hsc70); HBV; Hepatocellular carcinoma (HCC).

[448]

TÍTULO / TITLE: - Dual inhibition of MEK1/2 and EGFR synergistically induces caspase-3-dependent apoptosis in EGFR inhibitor-resistant lung cancer cells via BIM upregulation.

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

REVISTA / JOURNAL: - Invest New Drugs. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1007/s10637-013-0030-0](#)

AUTORES / AUTHORS: - Song JY; Kim CS; Lee JH; Jang SJ; Lee SW; Hwang JJ; Lim C; Lee G; Seo J; Cho SY; Choi J

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-2 dong, Songpa-gu, Seoul, 138-736, South Korea.

RESUMEN / SUMMARY: - Epidermal growth factor receptor (EGFR) gene mutations activate the KRAS-RAF-MEK-ERK pathway in lung cancer cells. EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib induce apoptosis of cancer cells, but prolonged

treatment is often associated with acquired resistance. Here, we identified a novel MEK1/2 inhibitor, CZ0775, and compared its cytotoxic effects to those of AZD6244 (selumetinib) in non-small cell lung cancer (NSCLC) cell lines harboring EGFR mutations. The lapatinib-sensitive HCC827 and PC9 and lapatinib-resistant H1650 and H1975 cell lines showed poor responses to CZ0775 and AZD6244 monotherapy with an IC50 > 10 µM. By contrast, combination treatment with lapatinib and CZ0775 inhibited cell proliferation and produced a 2-fold higher number of annexin V-labeled cells than lapatinib alone in H1975 cells. Furthermore, combination treatment decreased phosphorylated extracellular signal related kinase (p-ERK) and survivin levels and upregulated the expression of the pro-apoptotic protein BIM. siRNA-mediated BIM depletion reduced caspase-3 activity (~40 %) in lapatinib and CZ0775 treated H1975 cells. An in vitro ERK activity assay showed that p-ERK levels were approximately a 3-fold lower in H1975 cells treated with CZ0775 and lapatinib combination than in cells treated with lapatinib alone. CZ0775 was more cytotoxic than AZD6244 when used in combination with lapatinib. Our results suggest that combination treatment with CZ0775 and EGFR inhibitors is a promising therapeutic approach for the treatment of EGFR-TKI-resistant lung cancers and its effect is mediated by the inhibition of ERK and the induction of BIM.

[449]

TÍTULO / TITLE: - Keratin 17 in premalignant and malignant squamous lesions of the cervix: proteomic discovery and immunohistochemical validation as a diagnostic and prognostic biomarker.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Sep 20. doi: 10.1038/modpathol.2013.166.

●● [Enlace al texto completo \(gratis o de pago\) 1038/modpathol.2013.166](#)

AUTORES / AUTHORS: - Escobar-Hoyos LF; Yang J; Zhu J; Cavallo JA; Zhai H; Burke S; Koller A; Chen EI; Shroyer KR

INSTITUCIÓN / INSTITUTION: - 1] Department of Pharmacological Sciences, Stony Brook School of Medicine, Stony Brook, NY, USA [2] Department of Pathology, Stony Brook School of Medicine, Stony Brook, NY, USA [3] Department of Biology, Research Group Genetic Toxicology and Cytogenetics, Faculty of Natural Sciences and Education, Universidad del Cauca, Popayan, Colombia.

RESUMEN / SUMMARY: - Most previously described immunohistochemical markers of cervical high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma may help to improve diagnostic accuracy but have a minimal prognostic value. The goals of the current study were to identify and validate novel candidate biomarkers that could potentially improve diagnostic and prognostic accuracy for cervical HSIL and squamous cell carcinoma. Microdissected tissue sections from formalin-fixed paraffin-embedded normal ectocervical squamous mucosa, low-grade squamous intraepithelial

lesion (LSIL), HSIL and squamous cell carcinoma sections were analyzed by mass spectrometry-based shotgun proteomics for biomarker discovery. The diagnostic specificity of candidate biomarkers was subsequently evaluated by immunohistochemical analysis of tissue microarrays. Among 1750 proteins identified by proteomic analyses, keratin 4 (KRT4) and keratin 17 (KRT17) showed reciprocal patterns of expression in the spectrum of cases ranging from normal ectocervical squamous mucosa to squamous cell carcinoma. Immunohistochemical studies confirmed that KRT4 expression was significantly decreased in squamous cell carcinoma compared with the other diagnostic categories. By contrast, KRT17 expression was significantly increased in HSIL and squamous cell carcinoma compared with normal ectocervical squamous mucosa and LSIL. KRT17 was also highly expressed in immature squamous metaplasia and in endocervical reserve cells but was generally not detected in mature squamous metaplasia. Furthermore, high levels of KRT17 expression were significantly associated with poor survival of squamous cell carcinoma patients (Hazard ratio=14.76, P=0.01). In summary, both KRT4 and KRT17 expressions are related to the histopathology of the cervical squamous mucosa; KRT17 is highly overexpressed in immature squamous metaplasia, in HSIL, and in squamous cell carcinoma and the level of KRT17 in squamous cell carcinoma may help to identify patients who are at greatest risk for cervical cancer mortality. *Modern Pathology* advance online publication, 20 September 2013; doi:10.1038/modpathol.2013.166.

[450]

TÍTULO / TITLE: - Tropomyosin-related Kinase B Inhibitor Has Potential for Tumor Regression and Relapse Prevention in Pulmonary Large Cell Neuroendocrine Carcinoma.

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

REVISTA / JOURNAL: - *Anticancer Res.* 2013 Sep;33(9):3699-703.

AUTORES / AUTHORS: - Odate S; Onishi H; Nakamura K; Kojima M; Uchiyama A; Kato M; Katano M

INSTITUCIÓN / INSTITUTION: - Department of Cancer Therapy and Research, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. ohnishi@surg1.med.kyushu-u.ac.jp.

RESUMEN / SUMMARY: - Large cell neuroendocrine carcinoma (LCNEC) has an especially poor prognosis, and an effective therapeutic strategy has yet to be established. We have previously shown that the expressions of tropomyosin-related kinase B (TRKB) and brain-derived neurotrophic factor (BDNF) are high in LCNEC and that TRKB/BDNF signaling is involved in the proliferation, tumorigenesis, and invasive nature of LCNEC. Therefore, TRKB/BDNF signaling may offer a potential therapeutic target for LCNEC treatment. In the present study, we evaluated whether the TRKB tyrosine kinase inhibitor, k252a, has effects on tumor regression and relapse prevention on LCNEC,

using a murine xenograft model. The LCNEC cell line and NCI-H810 cells were subcutaneously implanted into the flanks or intrathoracically injected into the bilateral pleural cavities of BALB/c nude mice. k252a significantly inhibited tumor volume, expression of matrix metalloproteinases and the formation of pleural dissemination by LCNEC. These results suggest that k252a has potential for tumor regression and relapse prevention in LCNEC. Since many patients with LCNEC suffer through the use of ineffective therapeutic strategies, a clinical trial using the TRKB inhibitor for LCNEC is urgently required.

[451]

TÍTULO / TITLE: - The short chain cell-permeable ceramide (C6) restores cell apoptosis and perifosine sensitivity in cultured glioblastoma cells.

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

REVISTA / JOURNAL: - Mol Biol Rep. 2013 Sep 25.

●● Enlace al texto completo (gratis o de pago) 1007/s11033-013-2666-4

AUTORES / AUTHORS: - Qin LS; Yu ZQ; Zhang SM; Sun G; Zhu J; Xu J; Guo J; Fu LS

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, The First Affiliated Hospital of Soochow University, No. 188, Shi-zi Street, Suzhou, 215000, Jiangsu, People's Republic of China.

RESUMEN / SUMMARY: - Primary glioblastoma multiforme is the most malignant form of astrocytic tumor with an average survival of approximately 12-14 months. The combination of novel Akt inhibitors with anti-cancer therapeutics has achieved improved anti-tumor efficiency. In the current study, we examined the synergistic anti-cancer ability of Akt inhibitor perifosine in combination with short-chain ceramide (C6) against glioblastoma cells (U87MG and U251MG), and studied the underlying mechanisms. We found that perifosine, which blocked Akt/mammalian target of rapamycin activation, only induced moderate cell death and few cell apoptosis in cultured glioblastoma cells. On the other hand, perifosine administration induced significant protective autophagy, which inhibited cell apoptosis induction. Inhibition of autophagy by 3-methyladenine or by autophagy-related gene-5 RNA interference significantly enhanced perifosine-induced apoptosis and cytotoxicity. We found that the short chain cell-permeable ceramide (C6) significantly enhanced cytotoxic effects of perifosine in cultured glioblastoma cells. For mechanism study, we observed that ceramide (C6) inhibited autophagy induction to restore cell apoptosis and perifosine sensitivity. In conclusion, our study suggests that autophagy inhibition by ceramide (C6) restores perifosine-induced apoptosis and cytotoxicity in glioblastoma cells.

[452]

TÍTULO / TITLE: - Antiproliferative effect of alkylglycerols as vehicles of butyric acid on colon cancer cells.

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

REVISTA / JOURNAL: - Chem Phys Lipids. 2013 Aug 21;175-176C:50-56. doi: 10.1016/j.chemphyslip.2013.07.011.

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

[1016/j.chemphyslip.2013.07.011](#)

AUTORES / AUTHORS: - Molina S; Moran-Valero MI; Martin D; Vazquez L; Vargas T; Torres CF; Ramirez de Molina A; Reglero G

INSTITUCIÓN / INSTITUTION: - Imdea-Food Institute, CEI UAM+CSIC, 28049 Madrid, España.

RESUMEN / SUMMARY: - The anticarcinogenic activity of synthetic 1-O-octadecyl-2,3-dibutyroilglycerol (D-SCAKG) in tumor-cell line of colonocytes (SW620) was performed. The effect of the previously digested D-SCAKG under in vitro intestinal conditions was compared to the bioactivity of non-digested D-SCAKG. Antiproliferative activity of each individual product from digestion (1-O-octadecyl-2-butyroilglycerol; 1-O-octadecyl glycerol; butyric acid) was also performed. The impact of solubilization of lipid products within micellar structures was also tested. The 1-O-octadecyl glycerol was the most active compound, followed by 1-O-octadecyl-2-butyroilglycerol, D-SCAKG and butyric acid. The 1-O-octadecyl glycerol and butyric acid were the only molecules that showed antiproliferative effect in absence of micelles. Digested D-SCAKG was 4-fold more effective than non-digested D-SCAKG. A synergism between 1-O-octadecyl-2-butyroilglycerol and 1-O-octadecyl glycerol was evidenced. As summary, the synthetic D-SCAKG seems to be an interesting antitumoral lipid against colonocytes, especially after previous intestinal digestion, and mainly due to the synergism of the major products, namely 1-O-octadecyl-2-butyroilglycerol and 1-O-octadecyl glycerol. At the same time, 1-O-octadecyl-2-butyroilglycerol would constitute a stable esterified form of butyric acid for its vehiculization.

[453]

TÍTULO / TITLE: - Propofol induces apoptosis and increases gemcitabine sensitivity in pancreatic cancer cells in vitro by inhibition of nuclear factor-kappaB activity.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Sep 7;19(33):5485-92. doi: 10.3748/wjg.v19.i33.5485.

●● Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i33.5485](#)

AUTORES / AUTHORS: - Du QH; Xu YB; Zhang MY; Yun P; He CY

INSTITUCIÓN / INSTITUTION: - Qi-Hang Du, Yan-Bing Xu, Meng-Yuan Zhang, Peng Yun, Chang-Yao He, Department of Anesthesiology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan 250021, Shandong Province, China.

RESUMEN / SUMMARY: - AIM: To investigate the effect of propofol on human pancreatic cells and the molecular mechanism of propofol action. METHODS: We used the human pancreatic cancer cell line MIAPaCa-2 for in vitro studies measuring growth inhibition and degree of apoptotic cell death induced by propofol alone, gemcitabine alone, or propofol followed by gemcitabine. All experiments were conducted in triplicate and carried out on three or more separate occasions. Data were means of the three or more independent experiments +/- SE. Statistically significant differences were determined by two-tailed unpaired Student's t test and defined as $P < 0.05$. RESULTS: Pretreatment of cells with propofol for 24 h followed by gemcitabine resulted in 24%-75% growth inhibition compared with 6%-18% when gemcitabine was used alone. Overall growth inhibition was directly correlated with apoptotic cell death. We also showed that propofol potentiated gemcitabine-induced killing by downregulation of nuclear factor-kappaB (NF-kappaB). In contrast, NF-kappaB was upregulated when pancreatic cancer cells were exposed to gemcitabine alone, suggesting a potential mechanism of acquired chemoresistance. CONCLUSION: Inactivation of the NF-kappaB signaling pathway by propofol might abrogate gemcitabine-induced activation of NF-kappaB, resulting in chemosensitization of pancreatic tumors to gemcitabine.

[454]

TÍTULO / TITLE: - Long non-coding RNA HOTAIR, a driver of malignancy, predicts negative prognosis and exhibits oncogenic activity in oesophageal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 10. doi: 10.1038/bjc.2013.548.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.548](#)

AUTORES / AUTHORS: - Li X; Wu Z; Mei Q; Li X; Guo M; Fu X; Han W

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology, Institute of Basic Medicine, School of Life Sciences, Chinese PLA General Hospital, Beijing 100853, China.

RESUMEN / SUMMARY: - Background:HOX transcript antisense RNA (HOTAIR), which is expressed from the homebox C gene (HOXC) locus, is capable of reprogramming chromatin organisation and promoting cancer cell metastasis and can simultaneously bind the polycomb repressive complex 2, which enhances H3K27 trimethylation, and the LSD1-CoREST-REST complex, which is critical for H3K4 demethylation. Clinically, the overexpression of HOTAIR is a powerful predictor of the tumour progression and overall survival in patients with diverse cancers. The relationship between HOTAIR and oesophageal squamous cell carcinoma (ESCC), however, remains unclear. We investigated the role of HOTAIR in the pathogenesis of ESCC.Methods:We used quantitative real-time PCR to determine the level of HOTAIR in ESCC cell lines and 100 ESCC samples from patients; 56 adjacent non-neoplastic tissues were used as controls. We measured the effect of HOTAIR knockdown and overexpression in ESCC cell lines using colony formation assays, anchorage-independent growth assays, the CCK-8

assay, transwell migration and invasion assays, and Annexin V-binding assays. We analysed the growth of ESCC xenograft tumours in nude mice. Changes in the gene expression and methylation levels in ESCC cell lines were analysed using gene expression microarrays and the Infinium HumanMethylation450K BeadChip assay, respectively. Results: The levels of HOTAIR were increased in ESCC cell lines and patient samples compared with the controls; the expression levels correlated with the disease stage and survival time. The knockdown of HOTAIR in the KYSE510 and KYSE180 ESCC cell lines using small hairpin RNAs (shRNAs) reduced the ability of the cells to form foci, migrate, and invade the extracellular matrix in culture, altered cell cycle progression, and increased the sensitivity of the cells to apoptosis. The HOTAIR knockdown reduced cancer cell metastasis in vivo, and the tumours formed by HOTAIR-silenced ESCC cells were smaller, both in size and weight, than the tumours and metastases formed by the shRNA vector control cells in a mouse xenograft model. The results of the gene microarray study showed that HOTAIR reprogrammed the gene expression profile of ESCC cells, and the gene ontology analysis revealed an enrichment in genes that are important for tumorigenesis, such as genes involved in cell migration and the regulation of the cell cycle. Comparing the gene expression profiles and DNA methylation analysis between the KYSE180 and KYSE180_HOTAIR cells revealed that only a small proportion of the methylation changes were correlated with gene expression changes. Conclusion: HOX transcript antisense RNA is upregulated in ESCC cell lines and patient samples, and promotes ESCC cell proliferation and tumour metastasis in mice. The knockdown of HOTAIR resulted in significant changes in gene expression, and data analysis suggested that HOTAIR-mediated gene regulation has a critical role in ESCC progression and is a novel epigenetic molecular target for treating ESCC patients. British Journal of Cancer advance online publication, 10 September 2013; doi:10.1038/bjc.2013.548 www.bjcancer.com.

[455]

TÍTULO / TITLE: - Modulation of the response of prostate cancer cell lines to cisplatin treatment using small interfering RNA.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Oct;30(4):1936-42. doi: 10.3892/or.2013.2637. Epub 2013 Jul 24.

●● [Enlace al texto completo \(gratuito o de pago\) 3892/or.2013.2637](#)

AUTORES / AUTHORS: - Parra E; Ferreira J

INSTITUCIÓN / INSTITUTION: - Laboratory of Experimental Biomedicine, University of Tarapaca, Campus Esmeralda, Iquique, Chile.

RESUMEN / SUMMARY: - Cisplatin is one of the most effective and widely used chemotherapeutic agents against several types of human cancers. However, the underlying mechanisms of action are not fully understood. We aimed to investigate

the possible molecular mechanism(s) of acquired chemoresistance observed in prostate cancer cells treated with cisplatin. Human LNCaP cells (bearing wild-type p53) and PC-3 cells (lacking p53) were used. The expression levels of protein were determined by western blotting, and the mRNA levels were determined by reverse transcription-polymerase chain reaction (RT-PCR). Cell viability was measured by MTT assay, and the transcriptional effect of small interfering RNA (siRNA) was measured by luciferase reporter gene. We showed that cisplatin treatment increased JNK-1 and JNK-2 activity and expression in both LNCaP and PC-3 cells. In addition, the knockdown of JNK-1 expression by siRNA-JNK-1 or siRNA-JNK-2 significantly impaired the upregulation of AP-1 luciferase reporter gene, but failed to decrease the levels of AP-1 reporter gene expression induced by TPA treatment. Our observations indicate that JNK-1 and JNK-2 may be involved in the chemoresistance observed in prostate cancer cells treated with cisplatin and that blocking the stimulation of Jun kinase (JNK) signaling may be important for regulating the susceptibility to cisplatin of prostate cancer.

[456]

TÍTULO / TITLE: - Differential expression of p53 family proteins in colorectal adenomas and carcinomas: Prognostic and predictive values.

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

REVISTA / JOURNAL: - Histol Histopathol. 2013 Sep 2.

AUTORES / AUTHORS: - Bahnassy AA; Zekri AR; Salem SE; Abou-Bakr AA; Sakr MA; Abdel-Samiaa AG; Manal Al-Bradei M

INSTITUCIÓN / INSTITUTION: - Pathology Departments, National Cancer Institute, Cairo University, Cairo, Egypt. chaya2000@hotmail.com.

RESUMEN / SUMMARY: - Background: We studied the contribution of p53 family proteins and their isoforms to the development and progression of colorectal carcinoma in relation to VEGF. Methods: p53, p63, p73 and VEGF proteins were assessed in 45 colorectal adenomas (CRAs), 80 carcinomas (CRCs) and 36 normal colonic tissue samples (NCT) by immunohistochemistry. Different p63 and p73 isoforms were assessed by RT-PCR. Aberrant protein and RNA expressions were correlated to patients' characteristics, disease free and overall survival (DFS and OS). Results: p53, p63, p73 and VEGF proteins were detected in 22.2%, 73.3%, 33.3%, 46.7% CRAs; in 68.8%, 38.8%, 62.5%, 62.5% CRCs and 16.7%, 83.3%; 13.9%, 41.7% NCT (p0.05 except for VEGF). Commonest isoforms were TAp63alpha, DeltaNp63, TAp73alpha in CRA and DeltaNp63, TAp63alpha, DeltaNp73, TAp73beta in CRC. Significant correlations were found between aggressive tumor phenotypes and aberrations in p73, p53, p63, VEGF. DFS correlated with advanced stage, p73 and VEGF aberrations. While advanced stage, positive lymph nodes, p73 and p53 correlated with OS. Prognosis was worse in patients with aberrant p63 and p73 than in those with normal p63 and p73 expression

regardless of p53 gene status (p0.05). Conclusions: p53 family proteins and VEGF play a pivotal role in colorectal carcinogenesis. p53 prognostic potential is augmented by p73 and p63 aberrations indicating a synergistic effect between the three family members. Nodal status, stage, p73, VEGF and p53 could be used as predictors of DFS and OS.

[457]

TÍTULO / TITLE: - MicroRNA-100/99^a, deregulated in acute lymphoblastic leukaemia, suppress proliferation and promote apoptosis by regulating the FKBP51 and IGF1R/mTOR signalling pathways.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 12. doi: 10.1038/bjc.2013.562.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.562](#)

AUTORES / AUTHORS: - Li XJ; Luo XQ; Han BW; Duan FT; Wei PP; Chen YQ

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Gene Engineering of the Ministry of Education, State Key Laboratory for Biocontrol, School of Life Science, Sun Yat-sen University, Guangzhou 510275, China.

RESUMEN / SUMMARY: - Background:MicroRNAs alter multiple cell processes and thus influence tumour carcinogenesis and progression. MiR-100 and miR-99^a have been reported to be aberrantly expressed in acute leukaemia. In this study, we focused on their functions in acute lymphoblastic leukaemia (ALL) and the molecular networks in which they are involved.Methods:MiR-100 and miR-99^a expression levels were measured in acute leukaemia patients by qRT-PCR. Kaplan-Meier analysis and log-rank tests were used to calculate the survival rate. Three human ALL cell lines were studied. Apoptosis and proliferation were analysed using siRNA transfection, western blot and flow cytometry.Results:In vivo, miR-100 and miR-99^a were down-regulated in 111 ALL patients, especially in high-risk groups; their expression levels were correlated with the patient's 5-year survival. In vitro, the restoration of miR-100 and miR-99^a in ALL cells suppressed cell proliferation and increased dexamethasone-induced cell apoptosis. Ectopic expression of miR-100 and miR-99^a targeted FK506-binding protein 51 (FKBP51) and, in turn, influenced glucocorticoid receptor (GR) activity. Meanwhile, miR-100 and miR-99^a overexpression inhibited the expression of IGF1R and mTOR and their downstream oncogene MCL1.Conclusion:MiR-100 and miR-99^a have critical roles in altering cellular processes by targeting both the FKBP51 and IGF1R/mTOR signalling pathways in vitro and might represent a potential novel strategy for ALL treatment.British Journal of Cancer advance online publication, 12 September 2013; doi:10.1038/bjc.2013.562 www.bjcancer.com.

[458]

TÍTULO / TITLE: - miR-34^a suppresses mutagenesis by inducing apoptosis in human lymphoblastoid TK6 cells.

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

REVISTA / JOURNAL: - Mutat Res. 2013 Sep 8. pii: S1383-5718(13)00259-3. doi: 10.1016/j.mrgentox.2013.08.010.

●● Enlace al texto completo (gratis o de pago) 1016/j.mrgentox.2013.08.010

AUTORES / AUTHORS: - Chen X; Zhang Y; Yan J; Sadiq R; Chen T

INSTITUCIÓN / INSTITUTION: - Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, Food and Drug Administration, Jefferson, AR 72079, USA. Electronic address: xinrong.Chen@fda.hhs.gov.

RESUMEN / SUMMARY: - miR-34^a, a tumor suppressor miRNA, has been identified as a direct transcriptional target of P53. miRNA precursors and inhibitors have been used to modulate the expression of their targeted mRNA and thereby study miRNA functions. We indicated in our previous work that X-ray induces miR-34^a expression in a time and dose dependent manner. The objective of this study was to elucidate the role of miR-34^a in X-ray-induced mutations in human lymphoblast TK6 cells. Neither over-expression of miR-34^a by lipid transfection of miR-34^a precursor nor down regulation of endogenous miR-34^a by miR-34^a inhibitor had any effect on X-ray-induced micronucleus frequency in TK6 cells. Over-expression of miR-34^a in TK6 cells significantly reduced X-ray induced mutant frequency (MF) in the Thymidine Kinase (TK) locus while suppression of endogenous miR-34^a can increase the background level MF in TK6 cells. Furthermore, over-expression of miR-34^a promoted and down-regulation of miR-34^a inhibited background and X-ray-induced apoptosis in TK6 cells. Our study suggests miR-34^a is an important negative regulator of mutagenesis and the mechanism is possibly mediated through apoptosis.

[459]

TÍTULO / TITLE: - Selenium Compounds Induced ROS-Dependent Apoptosis in Myelodysplasia Cells.

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

REVISTA / JOURNAL: - Biol Trace Elem Res. 2013 Sep;154(3):440-7. doi: 10.1007/s12011-013-9749-x. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) 1007/s12011-013-9749-x

AUTORES / AUTHORS: - Goncalves AC; Barbosa-Ribeiro A; Alves V; Silva T; Sarmiento-Ribeiro AB

INSTITUCIÓN / INSTITUTION: - Applied Molecular Biology, University Clinic of Haematology and Center of Investigation in Environment, Genetics and Oncobiology (CIMAGO), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

RESUMEN / SUMMARY: - Several authors have demonstrated the chemoprotective and anti-carcinogenic role of selenium. However, the therapeutic potential of selenium in

myelodysplastic syndrome (MDS) as single agent and as co-adjuvant of the current therapies has not been previously studied. Sodium selenite and selenomethionine, alone and in combination with cytarabine, induce a decrease in cell viability in a time-, dose- and administration-dependent manner inducing cell death by apoptosis in F36P cells (MDS cell line). These compounds increased superoxide production and induced mitochondrial membrane depolarization. The increase in BAX/BCL-2 ratio and in the activated caspase 3 expression levels, the decrease in mitochondria membrane potential, as well as the increase in superoxide production, supports the mitochondria contribution on selenium-induced apoptosis. These findings suggest that selenium may offer a new therapeutic approach in myelodysplastic syndrome in monotherapy and/or as co-adjuvant therapy to conventional anti-carcinogenic.

[460]

TÍTULO / TITLE: - Loss of caspase 7 expression is associated with poor prognosis in renal cell carcinoma clear cell subtype.

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

REVISTA / JOURNAL: - Urology. 2013 Oct;82(4):974.e1-7. doi: 10.1016/j.urology.2013.06.026. Epub 2013 Aug 3.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.urology.2013.06.026](#)

AUTORES / AUTHORS: - Vilella-Arias SA; Rocha RM; da Costa WH; Zequi Sde C; Guimaraes GC; Verjovski-Almeida S; Soares FA; Reis EM

INSTITUCIÓN / INSTITUTION: - Departamento de Bioquímica, Instituto de Química, Universidade de Sao Paulo, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - **OBJECTIVE:** To investigate the expression of CASP7 protein in renal cell carcinoma clear cell subtype (ccRCC) and its value to predict cancer-specific survival (CSS). **METHODS:** A tissue microarray containing 120 samples of ccRCC, 45 non-ccRCC, and 66 nontumor paired samples from patients who underwent partial or radical nephrectomy was hybridized with anti-CASP7 antibody. Tissue sections were scored according to intensity and the percentage of stained cells. CASP7 immunostaining scores were used to estimate the association with clinicopathologic parameters and calculate Kaplan-Meier survival curves. **RESULTS:** Reduced CASP7 expression was observed in ccRCC and non-ccRCC subtypes in comparison with nontumor renal tissues ($P < .0001$). CASP7 immunostaining was associated ($P < .05$) with clinicopathologic parameters (size, incidental tumor, clinical stage, renal vein invasion, and tumor necrosis) and correlated with CSS ($P = .032$) and global survival ($P = .046$) of patients with ccRCC. In addition, CASP7 expression was able to stratify patients with ccRCC with favorable prognosis according to low clinical stage, in which negative CASP7 staining was associated with patients with lower CSS ($P = .045$). Finally, CASP7 staining was able to provide significant stratification according to CSS ($P = .018$) among patients with ccRCC with disease relapse. **CONCLUSION:** Our results implicate the loss

of CASP7 expression in the aggressiveness of ccRCC and indicate its potential use as a clinical prognostic marker of the disease.

[461]

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. 2013 Sep 20. doi: 10.4149/neo_2014_007.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2014_007](#)

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 a clinically 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 a sequential combination of PTX and RO3306, a cyclin-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 a synergistic 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.

[462]

TÍTULO / TITLE: - Novel o-naphthoquinones induce apoptosis of EL-4 T lymphoma cells through the increase of reactive oxygen species.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Oct;27(7):2094-2104. doi: 10.1016/j.tiv.2013.08.002. Epub 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.08.002](#)

AUTORES / AUTHORS: - Di Rosso ME; Barreiro Arcos ML; Elingold I; Sterle H; Baptista Ferreira S; Ferreira VF; Galleano M; Cremaschi G; Dubin M

INSTITUCIÓN / INSTITUTION: - Centro de Estudios Farmacológicos y Botánicos (CEFyBO), Facultad de Medicina, Universidad de Buenos Aires-CONICET, Paraguay 2155, Piso 16, C1121ABG Buenos Aires, Argentina.

RESUMEN / SUMMARY: - Novel beta-lapachone analogs 2-phenyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (NQ1), 2-p-tolyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (NQ3) and 2-methyl-2-phenyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione (NQ7), which have trypanocidal activity, were assayed for cytotoxic effects on murine EL-4 T lymphoma cells. The NQs inhibited the proliferation of EL-4 cells at concentrations above 1µM. Nuclear staining of the EL-4 cells revealed chromatin condensation and a nuclear morphology compatible with the induction of apoptosis. Flow cytometry assays with annexin V-FITC and propidium iodide confirmed the cell death by apoptosis. Using electron paramagnetic resonance (EPR), a semiquinone radical was detected in EL-4 cells treated with NQs. In addition, a decrease in the GSH level in parallel with reactive oxygen species (ROS) production was observed. Preincubation with n-acetyl-L-cysteine (NAC) was able to reverse the inhibitory effects of the NQs on cell proliferation, indicating that ROS generation is involved in NQ-induced apoptosis. In addition, the NQs induced a decrease in the mitochondrial membrane potential and increased the proteolytic activation of caspases 9 and 3 and the cleavage of Poly (ADP-Ribose) Polymerase (PARP). In conclusion, these results indicate that redox cycling is induced by the NQs in the EL-4 cell line, with the generation of ROS and other free radicals that could inhibit cellular proliferation as a result of the induction of the intrinsic apoptosis pathway.

[463]

TÍTULO / TITLE: - Zoledronic Acid-induced Cytotoxicity Through Endoplasmic Reticulum Stress Triggered REDD1-mTOR Pathway in Breast Cancer Cells.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3807-14.

AUTORES / AUTHORS: - Lan YC; Chang CL; Sung MT; Yin PH; Hsu CC; Wang KC; Lee HC; Tseng LM; Chi CW

INSTITUCIÓN / INSTITUTION: - Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Taipei 112, Taiwan. Tel: +886 228757535, lmtseng@vghtpe.gov.tw.

RESUMEN / SUMMARY: - BACKGROUND: Zoledronic acid (ZOL) used for the prevention/treatment of osteopathic complications has been reported to have antitumor effects in breast cancer treatment. However, little is known about the exact molecular mechanisms for antitumor actions of ZOL. In this study, two breast cancer cell lines were used to investigate the antitumor efficacy of ZOL and the underlying molecular mechanisms. RESULTS: The growth of two breast cancer cell lines was markedly decreased following treatment with ZOL. Compared with MCF-7 cells, MDA-MB-231 cells were more sensitive to ZOL treatment. Western blot analysis showed

that the inhibitory effect of zoledronic acid on growth was related to the extent of inhibition of phosphorylated-protein kinase B (p-AKT), and phosphorylated-mammalian target of rapamycin (p-mTOR). Moreover, the expression of the stress-responsive protein regulated in development and DNA damage response 1 (REDD1), an inhibitor of mTOR, was induced markedly to various degrees in different breast cancer cell lines after ZOL treatment. Interestingly, by examining the upstream signaling pathway of REDD1, we found that ZOL can induce endoplasmic reticulum stress responses through activating the protein kinase R (PKR)-related ER kinase-eukaryotic initiation factor 2 alpha-CCAAT/enhancer binding protein homologous protein (PERK-eIF2alpha-CHOP) pathway. CONCLUSION: Taken together, these results indicated that ZOL-induced cell death was caused by endoplasmic reticulum stress activating PERK-eIF2alpha-CHOP pathway to induce REDD1 expression and inhibit the mTOR pathway.

[464]

TÍTULO / TITLE: - Antiproliferative, Cell-Cycle Dysregulation Effects of Novel Asiatic Acid Derivatives on Human Non-small Cell Lung Cancer Cells.

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

REVISTA / JOURNAL: - Chem Pharm Bull (Tokyo). 2013 Oct 1;61(10):1015-1023. Epub 2013 Aug 6.

AUTORES / AUTHORS: - Wang L; Xu J; Zhao C; Zhao L; Feng B

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Dalian Medical University.

RESUMEN / SUMMARY: - Asiatic acid (AA) is a pentacyclic triterpene in *Centella asiatica* known to inhibit proliferation and induce apoptosis in several tumor cell lines. In the current study, we synthesized five AA derivatives and examined their inhibitory activities on growth in non-small cell lung cancer cell lines, A549 and PC9/G. Four derivatives were found to have stronger cell growth inhibitory activity than AA. Among them, compound A-3 showed the most significant antiproliferative effects on tumor. Growth of A549 and PC9/G cells was inhibited by A-3 in a dose- and time-dependent manner. To determine the cellular gene expression changes in A549 and PC9/G cells treated with A-3, Affymetrix GeneChip® Human Genome U133 Plus 2.0 Array were used to screen transcriptome differences. Expression levels of 1121 genes in A549 and 1873 genes in PC9/G were significantly altered upon treatment with 10 microM A-3 after 48 h, with 357 overlapping genes. The signaling pathways molecules involved in the antiproliferative and cell cycle dysregulation effects of A-3 identified using microarray were further validated via Western blot analyses. The results collectively indicate that A-3 induces inhibition of cell proliferation via downregulation of the Ras/Raf/MEK/ERK pathway and cell cycle arrest at G1/S and G2/M.

[465]

TÍTULO / TITLE: - A novel HDAC inhibitor OBP-801 and a PI3K inhibitor LY294002 synergistically induce apoptosis via the suppression of survivin and XIAP in renal cell carcinoma.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1080-6. doi: 10.3892/ijo.2013.2042. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2042](#)

AUTORES / AUTHORS: - Yamada T; Horinaka M; Shinnoh M; Yoshioka T; Miki T; Sakai T

INSTITUCIÓN / INSTITUTION: - Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.

RESUMEN / SUMMARY: - Renal cell carcinoma (RCC) is resistant to traditional cancer therapies such as radiation therapy and chemotherapy. The use of targeted therapies has improved the clinical outcomes of patients with metastatic RCC. However, most patients acquire resistance against targeted therapies over time. We report that the combination of the novel histone deacetylase (HDAC) inhibitor OBP-801, also known as YM753 and the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 synergistically inhibits cell growth and induces apoptosis in RCC cells. This combination activated caspase-3, -8 and -9 and the pan-caspase inhibitor zVAD-fmk significantly reduced the apoptotic response to the treatment with OBP-801 and LY294002. Moreover, the combined treatment induced intracellular reactive oxygen species (ROS) and the radical scavenger N-acetyl-L-cysteine (NAC) blocked the intracellular ROS and apoptosis induced by OBP-801 and LY294002. The co-treatment with OBP-801 and LY294002 markedly decreased survivin and the X-linked inhibitor of apoptosis protein (XIAP) protein levels, but Bcl-2 family members were not altered by the OBP-801/LY294002 co-treatment. These alterations were restored by NAC treatment. The transient transfection of survivin and XIAP reduced the apoptotic response to the OBP-801/LY294002 co-treatment. Additionally, OBP-801 was significantly more effective than SAHA, another HDAC inhibitor, in the combination with LY294002 against 786-O cells. Taken together, these results strongly suggest the combination of OBP-801 and LY294002 to be a promising treatment for RCC.

[466]

TÍTULO / TITLE: - Down-regulation of miR-145 and miR-143 might be associated with DNA methyltransferase 3B overexpression and worse prognosis in endometrioid carcinomas.

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

REVISTA / JOURNAL: - Hum Pathol. 2013 Sep 24. pii: S0046-8177(13)00289-X. doi: 10.1016/j.humpath.2013.07.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.humpath.2013.07.002](#)

AUTORES / AUTHORS: - Zhang X; Dong Y; Ti H; Zhao J; Wang Y; Li T; Zhang B

INSTITUCIÓN / INSTITUTION: - Department of Pathology, The Peking University, First Hospital, Beijing 100034, China.

RESUMEN / SUMMARY: - The aim of this study was to determine the clinicopathologic significance of miR-145 and miR-143 down-regulation in endometrial cancers. The microRNA profiles were analyzed by microRNA microarray. The expression levels of miR-145 and miR-143 in 73 endometrial cancers were further determined by quantitative real-time polymerase chain reaction. Potential targets of miR-145/143 were defined. The status of DNA methyltransferase 3B (DNMT3B), mutL homologs 1, and phosphatase and tensin homolog was assessed using immunohistochemistry. miR-145 and miR-143 frequently co-down-regulated in endometrial cancers, but the expression levels varied greatly between endometrioid carcinomas (ECs) and non-ECs (NECs); they were significantly lower in ECs than in NECs ($P < .05$). DNMT3B was defined as a potential target of miR-145/143 by Internet algorithms. In ECs, DNMT3B overexpression occurred more often in the miR-145 and miR-143 down-regulation subgroups, and the correlation between DNMT3B and miR-145 status reached statistical significance ($P = .021$), whereas such phenomena were not present in NECs ($P > .05$). In univariate analysis, the combination of DNMT3B overexpression and miR-145 or miR-143 down-regulation was more powerful in predicting shorter survival ($P < .05$) than use of the biomarkers individually ($P > .05$). In multivariate analysis, such combination was not an independent predictor of disease-free survival ($P > .05$). Our findings suggest that the target and function of miR-145 and miR-143 may differ in ECs versus NECs. DNMT3B might be a potential target of miR-145 and miR-143 in ECs. Furthermore, the combined miR-145 or miR-143 and DNMT3B status may have a prognostic impact on ECs.

[467]

TÍTULO / TITLE: - Enantiospecific Synthesis of Heterocycles Linked to Purines: Different Apoptosis Modulation of Enantiomers in Breast Cancer Cells.

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

REVISTA / JOURNAL: - Curr Med Chem. 2013 Sep 13.

AUTORES / AUTHORS: - Eugenia Garcia-Rubino M; Conejo-Garcia A; Nunez MC; Carrasco E; Garcia MA; Choquesillo-Lazarte D; Garcia-Ruiz JM; Gallo MA; Marchal JA; Campos JM

INSTITUCIÓN / INSTITUTION: - Departamento de Quimica Farmaceutica y Organica, Facultad de Farmacia, c/ Campus de Cartuja, s/n, 18071 Granada España.

jmcampos@ugr.es.

RESUMEN / SUMMARY: - The issue of chiral drug is now a major theme in the design, discovery and development of new drugs. It has been shown for many pharmaceuticals that only one enantiomer contains the desired activity, and the synthesis of such drug molecules in their optically pure form is becoming increasingly important. Mitsunobu

reaction was carried out between [®]- and (S)-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol and purines under microwave irradiation. A contraction into a six-membered ring takes place with concomitant inversion at the stereocentre with excellent enantiomeric excesses giving rise to the homochiral 9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9H-purines. The anti-tumour activity of all enantiomers is reported against the caspase-3-deficient MCF-7 and the wild type SKBR-3 human breast cancer cells. The most active homochiral compound displays an IC50 of 1.85 microM and induces inhibition of the translation initiation factor eIF2alpha. All homochiral compounds included in this study show different apoptotic effects between both enantiomers with levels up to 99%. We have analyzed caspase-mediated apoptotic pathways on enantiomers and racemates. We have found a homochiral derivative that activates the canonical intrinsic caspase-8/caspase-3 apoptotic pathway on the MCF-7 cells, and a racemic compound that induces caspase-2 activation. Moreover, we demonstrate the involvement of caspase activation during cell death induced by these compounds in SKBR-3 cells.

[468]

TÍTULO / TITLE: - Prognostic significance of sphingosine kinase 2 expression in non-small cell lung cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 7.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1051-1](#)

AUTORES / AUTHORS: - Wang Q; Li J; Li G; Li Y; Xu C; Li M; Xu G; Fu S

INSTITUCIÓN / INSTITUTION: - Department of Cardiothoracic Surgery, The Second Affiliated Hospital, Harbin Medical University, Harbin, 150086, China.

RESUMEN / SUMMARY: - Sphingosine kinase 2 (SphK2) as a conserved lipid kinase has not been thoroughly elucidated in non-small cell lung cancer (NSCLC). The aim of the present study was to evaluate the expression of SphK2 in NSCLC tissues and to determine its correlation with clinicopathologic characteristics and its impact on patient prognosis. We assessed the expression of SphK2 and proliferating cell nuclear antigen (PCNA) (as a proliferative index) by immunohistochemistry in 180 NSCLC patient's formalin-fixed paraffin-embedded tissue blocks. Relationship between the expression of SphK2 and PCNA and various clinicopathological features in these patients was evaluated. We detected that expression of SphK2 was gradually upregulated from normal, metaplasia/dysplasia tissues to NSCLC tissues. At the same time, PCNA expression followed a similar pattern. Statistical analysis showed that expression of SphK2 in NSCLC tissues was strongly associated with PCNA expression, histology grade, live vaccine strain invasion, lymph node status, clinical stage, tumors size, and histology type. Patients with SphK2 overexpression in their tissues had lower overall survival (OS) and disease-free survival (DFS) rates than those with low SphK2 expression. Using uni- and multivariate analysis, we found that SphK2 overexpression

was an independent prognostic factor for both OS and DFS. The expression of SphK2 parallels the progression of NSCLC, and SphK2 overexpression may represent a novel and potentially independent biomarker for the prognosis of patients with NSCLC.

[469]

TÍTULO / TITLE: - Prognostic Factors and Survival after Resection of Colorectal Liver Metastasis in the Era of Preoperative Chemotherapy: An 11-Year Single-Centre Study.

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

REVISTA / JOURNAL: - Dig Surg. 2013 Aug 21;30(4-5):293-301.

●● [Enlace al texto completo \(gratis o de pago\) 1159/000354310](#)

AUTORES / AUTHORS: - John SK; Robinson SM; Rehman S; Harrison B; Vallance A; French JJ; Jaques BC; Charnley RM; Manas DM; White SA

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary and Transplantation Surgery, Freeman Hospital, Newcastle upon Tyne, UK.

RESUMEN / SUMMARY: - Introduction: A variety of factors have been identified in the literature which influence survival following resection of colorectal liver metastases (CRLM). Much of this literature is historical, and its relevance to contemporary practice is not known. The aim of this study was to identify those factors which influence survival during the era of preoperative chemotherapy in patients undergoing resection of CRLM in a UK centre. Methods: All patients having liver resection for CRLM during an 11-year period up to 2011 were identified from a prospectively maintained database. Prognostic factors analysed included tumour size (≥ 5 or < 5 cm), lymph node status of the primary tumour, margin positivity (R1; < 1 mm), neo-adjuvant chemotherapy (for liver), tumour differentiation, number of liver metastases (≥ 4), preoperative carcinoembryonic antigen (CEA; ≥ 200 ng/ml) and whether metastases were synchronous (i.e. diagnosed within 12 months of colorectal resection) or metachronous to the primary tumour. Overall survival (OS) was compared using Kaplan-Meier plots and a log rank test for significance. Multivariate analysis was performed using a Cox regression model. Statistical analysis was performed in SPSS v19, and $p < 0.05$ was considered to be significant. Results: 432 patients underwent resection of CRLM during this period (67% male; mean age 64.5 years), and of these, 54 (13.5%) had re-resections. The overall 5-year survival in this series was 43% with an actuarial 10-year survival of 40%. A preoperative CEA ≥ 200 ng/ml was present in 10% of patients and was associated with a poorer 5-year OS (24 vs. 45%; $p < 0.001$). A positive resection margin < 1 mm was present in 16% of patients, and this had a negative impact on 5-year OS (15 vs. 47%; $p < 0.001$). Tumour differentiation, number, biliary or vascular invasion, size, relationship to primary disease, nodal status of the primary disease or the use of neo-adjuvant chemotherapy had no impact on OS. Multivariate analysis identified only the presence of a positive resection margin (OR 1.75; $p < 0.05$) and a preoperative CEA ≥ 200 ng/ml (OR 1.88; $p < 0.01$) as

independent predictors of poor OS. Conclusion: Despite the wide variety of prognostic factors reported in the literature, this study was only able to identify a preoperative CEA ≥ 200 ng/ml and the presence of tumour within 1 mm of the resection margin as being of value in predicting survival. These variables are likely to identify patients who may benefit from intensive follow-up to enable early aggressive treatment of recurrent disease. © 2013 S. Karger AG, Basel.

[470]

TÍTULO / TITLE: - Up-regulation of NEK2 by MicroRNA-128 Methylation is Associated with Poor Prognosis in Colorectal Cancer.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Sep 18.

●● [Enlace al texto completo \(gratis o de pago\) 1245/s10434-013-3264-3](#)

AUTORES / AUTHORS: - Takahashi Y; Iwaya T; Sawada G; Kurashige J; Matsumura T; Uchi R; Ueo H; Takano Y; Eguchi H; Sudo T; Sugimachi K; Yamamoto H; Doki Y; Mori M; Mimori K

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Beppu Hospital, Kyushu University, Beppu, Japan.

RESUMEN / SUMMARY: - BACKGROUND: NIMA-related kinase 2 (NEK2), an enzyme involved in the development and progression of cancer, is abnormally expressed in a wide variety of human cancers, including colorectal cancer (CRC), and is known to have roles in cell division and mitotic regulation through centrosome splitting. We investigated the clinical significance of NEK2 in CRC. In particular, we examined miR-128 expression, which is thought to target NEK2. METHODS: We measured NEK2 mRNA and miR-128 levels in clinical samples by quantitative reverse transcription real-time PCR and analyzed the associations between NEK2 levels, miR-128 levels, clinicopathological factors, and prognoses. Furthermore, we performed in vitro assays using a pre-miR-128 precursor and conducted miR-128 methylation analyses. RESULTS: MiR-128 inhibited NEK2 expression and cancer cell proliferation via cell cycle arrest. Moreover, miR-128 was silenced by DNA methylation. Increased NEK2 expression was associated with serosal invasion, lymphatic invasion, and peritoneal dissemination. Patients with high NEK2 expression also had significantly poorer prognoses. Multivariate analysis indicated that high NEK2 expression was an independent prognostic factor for survival. Patients with high miR-128 expression had significantly lower NEK2 expression and lower recurrence rates than those with low miR-128 expression. CONCLUSIONS: NEK2 may be an independent prognostic factor for CRC and was regulated by miR-128, a microRNA that was subjected to epigenetic regulation. Thus, this miR-128/NEK2 pathway may be a prospective therapeutic target for patients with CRC.

[471]

TÍTULO / TITLE: - Valproic acid enhances fludarabine-induced apoptosis mediated by ROS and involving decreased AKT and ATM activation in B-cell-lymphoid neoplastic cells.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Sep 22.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0906-7](#)

AUTORES / AUTHORS: - Yoon JY; Ishdorj G; Graham BA; Johnston JB; Gibson SB

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, MB, Canada.

RESUMEN / SUMMARY: - Histone deacetylase (HDAC) inhibitors have been shown synergize with a number of cytotoxic drugs in leukemic cells. In chronic lymphocytic leukemia (CLL), the first line therapy is based on the combination of fludarabine, a nucleoside analogue, and rituximab, an anti-CD20 monoclonal antibody, and there are presently no HDAC inhibitors are used to manage CLL. In the present study, we found that the addition of valproic acid (VPA), a HDAC inhibitor, increases cell death in B-cell-neoplasm-derived cell lines, BJAB, NALM-6 and I-83. This increased apoptosis caused release of mitochondrial cytochrome c, activation of caspases, and increased reactive oxygen species (ROS). The addition of a ROS scavenger inhibited cell death induced by the VPA-fludarabine combination. In contrast, blocking the death receptor pathway failed to inhibit VPA increased fludarabine induced apoptosis. Combination of VPA and fludarabine treatment decreased both total and phosphorylated levels of AKT, an important anti-apoptotic protein, and ATM, a pivotal protein in DNA damage response. Chemical inhibition of AKT or ATM was sufficient to enhance fludarabine-induced apoptosis. We next examined patient samples from a local clinical trial where relapsed CLL patients were treated with VPA and examined the effects of VPA on AKT and ATM in vivo. After 30 days, there was a reduction in ATM levels in three out of the four patients treated, while AKT phosphorylation was reduced only in one patient. Taken together, VPA reduces ATM levels, thereby increasing ROS-dependent cell death via the mitochondrial apoptotic pathway when combined with fludarabine.

[472]

TÍTULO / TITLE: - alpha-Mangostin induces mitochondrial dependent apoptosis in human hepatoma SK-Hep-1 cells through inhibition of p38 MAPK pathway.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0888-5](#)

AUTORES / AUTHORS: - Hsieh SC; Huang MH; Cheng CW; Hung JH; Yang SF; Hsieh YH

INSTITUCIÓN / INSTITUTION: - Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, ROC.

RESUMEN / SUMMARY: - alpha-Mangostin is a dietary xanthone that has been shown to have anti-cancer and anti-proliferative properties in various types of human cancer cells. This study investigates the molecular mechanism of the apoptosis-inducing effects of alpha-mangostin on human hepatocellular carcinoma (HCC) cells. We observed that alpha-mangostin reduces the viability of HCC cells in a dose- and time-dependent manner. alpha-Mangostin mediated apoptosis of SK-Hep-1 cells is accompanied by nuclear chromatin condensation and cell cycle arrest in the sub-G1 phases as well as phosphatidylserine exposure. Furthermore, alpha-mangostin triggered the mitochondrial caspase apoptotic pathway, as indicated by the loss of mitochondrial membrane potential, the release of cytochrome c from mitochondria, and the regulation of B cell lymphoma 2 family member expression. Moreover, alpha-mangostin inhibited a sustained activation of p38 mitogen-activated protein kinase (MAPK) phosphorylation, and treatment with a p38 MAPK inhibitor enhanced alpha-mangostin-induced caspase activation and apoptosis in SK-Hep-1 cells. In vivo xenograft mice experiments revealed that alpha-mangostin significantly reduced tumor growth and weight in mice inoculated with SK-Hep-1 cells. These findings demonstrate that alpha-mangostin induces mitochondria-mediated apoptosis through inactivation of the p38 MAPK signaling pathway and that alpha-mangostin inhibits the in vivo tumor growth of SK-Hep-1 xenograft mice.

[473]

TÍTULO / TITLE: - Superoxide activates mTOR-eIF4E-Bax route to induce enhanced apoptosis in leukemic cells.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Sep 20.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0904-9](#)

AUTORES / AUTHORS: - Chaudhuri J; Chowdhury AA; Biswas N; Manna A; Chatterjee S; Mukherjee T; Chaudhuri U; Jaisankar P; Bandyopadhyay S

INSTITUCIÓN / INSTITUTION: - Division of Cancer Biology and Inflammatory Disorder, Council of Scientific and Industrial Research (CSIR)-Indian Institute of Chemical Biology (IICB), 4, Raja S.C. Mullick Road, Jadavpur, Kolkata, 700032, India.

RESUMEN / SUMMARY: - Mammalian target of rapamycin (mTOR) is a central kinase that regulates cell survival, proliferation and translation. Reactive oxygen species (ROS) are second messengers with potential in manipulating cellular signaling. Here we report that two ROS generating phytochemicals, hydroxychavicol and curcumin synergize in leukemic cells in inducing enhanced apoptosis by independently activating both mitogen activated protein kinase (MAPK) (JNK and P38) and mTOR pathways. Low level transient ROS generated after co-treatment with these phytochemicals led to activation of these two pathways. Both mTOR and MAPK pathways played important roles in co-treatment-induced apoptosis, by knocking down either mTOR or MAPKs

inhibited apoptosis. Activation of mTOR, as evident from phosphorylation of its downstream effector eukaryotic translation initiation factor 4E-binding protein 1, led to release of eukaryotic translation initiation factor 4E (eIF4E) which was subsequently phosphorylated by JNK leading to translation of pro-apoptotic proteins Bax and Bad without affecting the expression of anti-apoptotic protein Bcl-xl. Our data suggest that mTOR and MAPK pathways converge at eIF4E in co-treatment-induced enhanced apoptosis and provide mechanistic insight for the role of mTOR activation in apoptosis.

[474]

TÍTULO / TITLE: - A study on the role of (+)-catechin in suppression of HepG2 proliferation via caspase dependent pathway and enhancement of its in vitro and in vivo cytotoxic potential through liposomal formulation.

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

REVISTA / JOURNAL: - Eur J Pharm Sci. 2013 Nov 20;50(3-4):353-365. doi: 10.1016/j.ejps.2013.08.005. Epub 2013 Aug 15.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejps.2013.08.005](#)

AUTORES / AUTHORS: - Jain P; Kumar N; Josyula VR; Jagani HV; Udupa N; Mallikarjuna Rao C; Vasanth Raj P

INSTITUCIÓN / INSTITUTION: - Cell and Molecular Biology Lab, Department of Pharmaceutical Biotechnology, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka 576104, India.

RESUMEN / SUMMARY: - Catechin is a known hepatoprotective and anticancer agent but has limited bioavailability. Its apoptotic signaling pathway in human hepatocellular carcinoma is vaguely explored. Thus, this study was designed to explore cytotoxicity by MTT assay, induction of apoptosis via DNA fragmentation, nuclear staining, bivariate flow cytometric analysis using annexin V- FITC and propidium iodide, cell cycle analysis and apoptotic markers by RT-PCR and western blotting in HepG2 cells. To increase the bioavailability and selectivity to cancer cells, various liposomes of catechin viz., conventional, charged and PEGylated forms were prepared by film hydration method and evaluated for cytotoxicity in vitro in HepG2 cells and in vivo in EAC-induced liquid tumor model. Catechin and catechin liposomes inhibited the growth of HepG2 cell lines at concentrations 100-200µg/mL depending on the length of exposure. It induced apoptosis and inhibited G2/M phase in cell cycle analysis. Catechin downregulated Bcl-2, initiated the release of cytochrome c into the cytosol and upregulated Bax, caspase-3,-9 and p53 in the HepG2 cells. Catechin and its liposomal formulation, at a dose of 200mg/kg body weight was found to be significantly ($p < 0.05$) effective in inhibiting percentage increase in body weight and enhancing the mean survival time. Deviated hematological parameters, antioxidant parameters (superoxide dismutase, catalase and lipid peroxidation) and LFT in tumor bearing mice were found

to be significantly ($p < 0.05$) restored towards normal after treatment with catechin and its liposomes.

[475]

TÍTULO / TITLE: - Enhanced cytotoxicity of pentachlorophenol by perfluorooctane sulfonate or perfluorooctanoic acid in HepG2 cells.

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

REVISTA / JOURNAL: - Chemosphere. 2013 Aug 22. pii: S0045-6535(13)01038-2. doi: 10.1016/j.chemosphere.2013.07.054.

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

[1016/j.chemosphere.2013.07.054](#)

AUTORES / AUTHORS: - Shan G; Ye M; Zhu B; Zhu L

INSTITUCIÓN / INSTITUTION: - College of Environmental Science and Engineering, Tianjin Key Laboratory of Urban Ecology Environmental Remediation and Pollution Control, Nankai University, Tianjin 300071, PR China.

RESUMEN / SUMMARY: - Chlorinated phenols and perfluoroalkyl acids (PFAAs) are two kinds of pollutants which are widely present in the environment. Considering liver is the primary toxic target organ for these two groups of chemicals, it is interesting to evaluate the possible joint effects of them on liver. In this work, the combined toxicity of pentachlorophenol (PCP) and perfluorooctane sulfonate (PFOS) or perfluorooctanoic acid (PFOA) were investigated using HepG2 cells. The results indicated that PFOS and PFOA could strengthen PCP's hepatotoxicity. Further studies showed that rather than intensify the oxidative stress or promote the biotransformation of PCP, PFOS (or PFOA) might lead to strengthening of the oxidative phosphorylation uncoupling of PCP. By measuring the intracellular PCP concentration and the cell membrane properties, it was suggested that PFOS and PFOA could disrupt the plasma membrane and increase the membrane permeability. Thus, more cellular accessibility of PCP was induced when they were co-exposed to PCP and PFOS (or PFOA), leading to increased cytotoxicity. Further research is warranted to better understand the combined toxicity of PFAAs and other environmental pollutants.

[476]

TÍTULO / TITLE: - Stabilization of the integrase-DNA complex by Mg ions and prediction of key residues for binding HIV-1 integrase inhibitors.

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

REVISTA / JOURNAL: - Proteins. 2013 Sep 5. doi: 10.1002/prot.24412.

●● Enlace al texto completo (gratis o de pago) [1002/prot.24412](#)

AUTORES / AUTHORS: - Miri L; Bouvier G; Kettani A; Mikou A; Wakrim L; Nilges M; Malliavin TE

INSTITUCIÓN / INSTITUTION: - Laboratoire de Virologie, Institut Pasteur du Maroc, 1, Place Louis Pasteur, 20360, Casablanca, Morocco; Unite de modelisation moleculaire et d'ingenierie des biomolecules, Laboratoire de recherche sur les lipoproteines et l'atherosclerose, Unite Associee au CNRST- URAC34. Faculte des Sciences Ben M'Sik, Casablanca, Morocco.

RESUMEN / SUMMARY: - The HIV-1 integrase is an attractive target for the therapeutics development against AIDS, as no host homologue of this protein has been identified. The integrase strand transfer inhibitors (INSTIs), including raltegravir, specifically target the second catalytic step of the integration process by binding to the DDE motif of the catalytic site and coordinating Mg²⁺ ions. Recent X-ray crystallographic structures of the integrase/DNA complex from prototype foamy virus allowed to investigate the role of the different partners (integrase, DNA, Mg²⁺ ions, raltegravir) in the complex stability using molecular dynamics (MD) simulations. The presence of Mg²⁺ ions is found to be essential for the stability, whereas the simultaneous presence of raltegravir and Mg²⁺ ions has a destabilizing influence. A homology model of HIV-1 integrase was built on the basis of the X-ray crystallographic information, and protein marker residues for the ligand binding were detected by clustering the docking poses of known HIV-1 integrase inhibitors on the model. Interestingly, we had already identified some of these residues to be involved in HIV-1 resistance mutations and in the stabilization of the catalytic site during the MD simulations. Classification of protein conformations along MD simulations, as well as of ligand docking poses were performed by using an original learning method, based on self-organizing maps. This allows us to perform a more in-depth investigation of the free-energy basins populated by the complex in MD simulations on the one hand, and a straightforward classification of ligands according to their binding residues on the other. © Proteins 2013. Esta es una cita bibliográfica que va por delante de la publicación en papel. La fecha indicada en la cita provista, NO corresponde con la fecha o la cita bibliográfica de la publicación en papel. La cita bibliográfica definitiva (con el volumen y su paginación) saldrá en 1 ó 2 meses a partir de la fecha de la emisión electrónica-online. *** This is a bibliographic record ahead of the paper publication. The given date in the bibliographic record does not correspond to the date or the bibliographic citation on the paper publication. The publisher will provide the final bibliographic citation (with the volume, and pagination) within 1 or 2 months from the date the record was published online. © 2013 Wiley Periodicals, Inc.

[477]

TÍTULO / TITLE: - Biophysical basis of the promiscuous binding of B-cell lymphoma protein 2 apoptotic repressor to BH3 ligands.

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

REVISTA / JOURNAL: - J Mol Recognit. 2013 Oct;26(10):501-13. doi: 10.1002/jmr.2295.

- Enlace al texto completo (gratis o de pago) [1002/jmr.2295](https://doi.org/10.1002/jmr.2295)

AUTORES / AUTHORS: - Bhat V; Olenick MB; Schuchardt BJ; Mikles DC; McDonald CB; Farooq A

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry & Molecular Biology, Miller School of Medicine, University of Miami, Miami, FL, 33136, USA.

RESUMEN / SUMMARY: - B-cell lymphoma protein 2 (Bcl2) apoptotic repressor carries out its function by virtue of its ability to bind to BH3 domains of various pro-apoptotic regulators in a highly promiscuous manner. Herein, we investigate the biophysical basis of such promiscuity of Bcl2 toward its cognate BH3 ligands. Our data show that although the BH3 ligands harboring the LXXXAD motif bind to Bcl2 with submicromolar affinity, those with the LXXX[G/S]D motif afford weak interactions. This implies that the replacement of alanine at the fourth position (A + 4)-relative to the N-terminal leucine (L0) within the LXXXAD motif-to glycine/serine results in the loss of free energy of binding. Consistent with this notion, the A + 4 residue within the BH3 ligands harboring the LXXXAD motif engages in key intermolecular van der Waals contacts with A149 lining the ligand binding groove within Bcl2, whereas A + 4G/S substitution results in the disruption of such favorable binding interactions. Of particular interest is the observation that although increasing ionic strength has little or negligible effect on the binding of high-affinity BH3 ligands harboring the LXXXAD motif, the binding of those with the LXXX[G/S]D motif in general experiences a varying degree of enhancement. This salient observation is indicative of the fact that hydrophobic forces not only play a dominant but also a universal role in driving the Bcl2-BH3 interactions. Taken together, our study sheds light on the molecular basis of the factors governing the promiscuous binding of Bcl2 to pro-apoptotic regulators and thus bears important consequences on the development of rational therapeutic approaches. Copyright © 2013 John Wiley & Sons, Ltd.

[478]

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 Sep 26.

- Enlace al texto completo (gratis o de pago) [2967/jnumed.113.126342](https://doi.org/10.1097/jnumed.113.126342)

AUTORES / AUTHORS: - Kenny LM

INSTITUCIÓN / INSTITUTION: - Imperial College London London, United Kingdom.

[479]

TÍTULO / TITLE: - Improved cytotoxic T-lymphocyte immune responses to a tumor antigen by vaccines co-expressing the SLAM-associated adaptor EAT-2.

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

REVISTA / JOURNAL: - Cancer Gene Ther. 2013 Aug 16. doi: 10.1038/cgt.2013.53.

●● Enlace al texto completo (gratis o de pago) [1038/cgt.2013.53](#)

AUTORES / AUTHORS: - Aldhamen YA; Seregin SS; Kousa YA; Rastall DP; Appledorn DM; Godbehere S; Schutte BC; Amalfitano A

INSTITUCIÓN / INSTITUTION: - Department of Microbiology and Molecular Genetics, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA.

RESUMEN / SUMMARY: - The signaling lymphocytic activation molecule-associated adaptor Ewing's sarcoma's-activated transcript 2 (EAT-2) is primarily expressed in dendritic cells, macrophages and natural killer cells. Including EAT-2 in a vaccination regimen enhanced innate and adaptive immune responses toward pathogen-derived antigens, even in the face of pre-existing vaccine immunity. Herein, we investigate whether co-vaccinations with two recombinant Ad5 (rAd5) vectors, one expressing the carcinoembryonic antigen (CEA) and one expressing EAT-2, can induce more potent CEA-specific cytotoxic T lymphocyte (CTL) and antitumor activity in the therapeutic CEA-expressing MC-38 tumor model. Our results suggest that inclusion of EAT-2 significantly alters the kinetics of Th1-biasing proinflammatory cytokine and chemokine responses, and enhances anti-CEA-specific CTL responses. As a result, rAd5-EAT2-augmented rAd5-CEA vaccinations are more efficient in eliminating CEA-expressing target cells as measured by an in vivo CTL assay. Administration of rAd5-EAT2 vaccines also reduced the rate of growth of MC-38 tumor growth in vivo. Also, an increase in MC-38 tumor cell apoptosis (as measured by hematoxylin and eosin staining, active caspase-3 and granzyme B levels within the tumors) was observed. These data provide evidence that more efficient, CEA-specific effector T cells are generated by rAd5 vaccines expressing CEA, when augmented by rAd5 vaccines expressing EAT-2, and this regimen may be a promising approach for cancer immunotherapy in general. Cancer Gene Therapy advance online publication, 16 August 2013; doi:10.1038/cgt.2013.53.

[480]

TÍTULO / TITLE: - Targeting heat-shock-protein 90 (Hsp90) by natural products: geldanamycin, a show case in cancer therapy.

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

REVISTA / JOURNAL: - Nat Prod Rep. 2013 Oct 11;30(10):1299-323. doi: 10.1039/c3np70012g. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1039/c3np70012g](#)

AUTORES / AUTHORS: - Franke J; Eichner S; Zeilinger C; Kirschning A

INSTITUCIÓN / INSTITUTION: - Institut für Organische Chemie und Zentrum für Biomolekulare Wirkstoffchemie (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany. andreas.kirschning@oci.uni-hannover.de.

RESUMEN / SUMMARY: - Covering: 2005 to 2013 In this review recent progress in the development of heat shock proteins (Hsp90) in oncogenesis is illuminated. Particular emphasis is put on inhibitors such as geldanamycin and analogues that serve as a natural product show case. Hsp90 has emerged as an important target in cancer therapy and/or against pathogenic cells which elicit abnormal Hsp patterns. Competition for ATP by geldanamycin and related compounds abrogate the chaperone function of Hsp90. In this context, this account pursues three topics in detail: a) Hsp90 and its biochemistry, b) Hsp90 and its role in oncogenesis and c) strategies to create compound libraries of structurally complex inhibitors like geldanamycin on which SAR studies and the development of drugs that are currently in different stages of clinical testing rely.

[481]

TÍTULO / TITLE: - Magnolol induces apoptosis via caspase-independent pathways in non-small cell lung cancer cells.

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

REVISTA / JOURNAL: - Arch Pharm Res. 2013 Aug 14.

●● Enlace al texto completo (gratis o de pago) [1007/s12272-013-0232-1](#)

AUTORES / AUTHORS: - Tsai JR; Chong IW; Chen YH; Hwang JJ; Yin WH; Chen HL; Chou SH; Chiu CC; Liu PL

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, No. 100, Shih-Chuan 1st Road, Kao-hsiung, 80708, Taiwan.

RESUMEN / SUMMARY: - Magnolol, a hydroxylated biphenyl agent isolated from herbal plant *Magnolia officinalis*, is a component of traditional Asian herbal teas. It has been reported to have anti-microbial, anti-inflammatory, and anti-cancer activity. Non-small cell lung cancer (NSCLC) cell lines (A549, H441 and H520) and normal human bronchial epithelial cells (HBECs) were used to evaluate the cytotoxic effect of magnolol. We show that magnolol inhibited cellular proliferation, increased DNA fragmentation, and decreased mitochondrial membrane potential in all NSCLC cells, but had no cytotoxic effect on HBECs. Magnolol triggered the release of pro-apoptotic proteins: Bid, Bax and cytochrome c from mitochondria, but did not activate the caspase-3, -8, and -9, suggesting that magnolol induces apoptosis of NSCLC cell lines via a caspase-independent pathway. The caspase-independent pathway is mediated through the activation of nuclear translocation of apoptosis-inducing factor, endonuclease G and cleaved poly(ADP-ribose) polymerase, which played important roles in mediating cell death. Furthermore, magnolol inhibited PI3K/AKT and ERK1/2 activity, but up-

regulated p38 and JNK activity in A549 cell lines. The results of this study provided a basis for understanding and developing magnolol as a novel treatment of NSCLC.

[482]

TÍTULO / TITLE: - Anticancer activity of an antisense oligonucleotide targeting TRADD combined with proteasome inhibitors in chemoresistant hepatocellular carcinoma cells.

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

REVISTA / JOURNAL: - J Chemother. 2013;25(5):292-7. doi: 10.1179/1973947813Y.0000000087.

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

[1179/1973947813Y.0000000087](#)

AUTORES / AUTHORS: - Witort E; Lulli M; Carloni V; Capaccioli S

INSTITUCIÓN / INSTITUTION: - University of Florence, Italy.

RESUMEN / SUMMARY: - Chemoresistance is a major cause of mortality of patients with advanced and metastatic hepatocellular carcinoma (HCC), the fifth most common cancer in the world. We employed a molecular approach to inhibit cell proliferation and induce apoptosis in HepG2 cells, originated from human hepatocarcinoma. TRADD gene expression was knocked down by an antisense oligonucleotide (ASO TRADD), resulting in TRADD protein decrease by 60%, coinciding with increase of apoptotic cell death of up to 30%. Combination of the ASO TRADD with the cytotoxic drugs 5-fluorouracil or paclitaxel did not improve chemosensitivity of HepG2 cells, while the combined administration of the ASO TRADD with proteasome inhibitors MG132 or ALLN inhibited cell proliferation by 80% and 93%, respectively. Taken together, these findings reveal the importance to combine proteasome inhibitors with silencing of anti-apoptotic signalling components to target HCC cells effectively and provide useful data for developing potential treatments of HCC.

[483]

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. 2013 Sep 20. doi: 10.4149/neo_2014_009.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2014_009](#)

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 INCB01424 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.

[484]

TÍTULO / TITLE: - Comparison of tuberculosis incidence in ankylosing spondylitis and rheumatoid arthritis during tumor necrosis factor inhibitor treatment in an intermediate burden area.

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

REVISTA / JOURNAL: - Clin Rheumatol. 2013 Sep 22.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10067-013-2387-z](#)

AUTORES / AUTHORS: - Kim HW; Park JK; Yang JA; Yoon YI; Lee EY; Song YW; Kim HR; Lee EB

INSTITUCIÓN / INSTITUTION: - Division of Rheumatology, Department of Internal Medicine, Eulji University School of Medicine, Eulji General Hospital, Seoul, South Korea.

RESUMEN / SUMMARY: - Clinical characteristics of antitumor necrosis factor (TNF) agents-related tuberculosis (TB) in ankylosing spondylitis (AS) are not well described. The aim was to compare the incidences and the characteristics of TB in AS and rheumatoid arthritis (RA) during TNF inhibitor treatment. AS (n = 1,322) and RA (n = 3,154) patients who received medical care between January 2001 and August 2011 were enrolled. The incidence of TB in patients treated, or not, with TNF inhibitors and the clinical features associated with TB were explored. Seven patients with AS and seven with RA developed TB while receiving TNF inhibitor therapy, resulting in an incidence rate of 600.2/100,000 person-years (PYs) (95 % confidence interval (CI),

241.3-1236.3) for those with AS and 771.6/100,000 PYs (95 % CI, 310.2-1589.9) for those with RA. Incidence rate ratios for TNF inhibitor-treated vs. untreated patients were 4.87 for AS (95 % CI, 1.50-15.39; $p < 0.001$) and 3.61 for RA (95 % CI, 1.38-8.07; $p < 0.001$). Low body mass index was identified as a significant risk factor for TB in the AS group (odds ratio (OR), 13.0; $p = 0.002$). Extrapulmonary TB was predominant at 85.7 % during TNF inhibitor treatment. Three (42.8 %) of the AS patients, but none of the RA patients, developed TB with concomitant isoniazid. All AS patients recovered from TB whereas two of seven RA patients died. Treatment with TNF inhibitors significantly increases the risk of extrapulmonary TB in AS. Symptoms of infection should warrant clinicians to evaluate for TB during TNF inhibitor therapy in AS patients.

[485]

TÍTULO / TITLE: - Circulating Tumor Cell (CTC) Count and Epithelial Growth Factor Receptor Expression on CTCs as Biomarkers for Cetuximab Efficacy in Advanced Colorectal Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3905-10.

AUTORES / AUTHORS: - Kuboki Y; Matsusaka S; Minowa S; Shibata H; Suenaga M; Shinozaki E; Mizunuma N; Ueno M; Yamaguchi T; Hatake K

INSTITUCIÓN / INSTITUTION: - Gastroenterological Center, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan. satoshi.matsusaka@jfc.or.jp.

RESUMEN / SUMMARY: - Background/Aim: The purpose of this study was to establish whether CTC count and epidermal growth factor receptor (EGFR) expression in CTCs predicted outcome in patients with advanced colorectal cancer (ACC) receiving cetuximab as third-line treatment. PATIENTS AND METHODS: Between October 2008 and March 2011, 63 patients with KRAS wild-type ACC were treated with cetuximab-containing chemotherapy at the Cancer Institute Hospital. We measured the CTC count and EGFR expression on CTCs using the CellSearch System (Veridex LLC, NJ, USA). RESULTS: Nineteen patients (30%) with a high number of CTCs had a significantly lower overall survival compared with 44 patients with a low number of CTCs. No significant difference was observed in progression-free survival between the two groups. Out of the 33 patients positive for CTCs (one or more CTC), seven patients (21%) were positive for EGFR expression. No statistically significant difference was observed in clinical outcome between EGFR-positive and EGFR-negative patients. CONCLUSION: A high CTC count predicted reduced overall survival in patients with ACC treated with cetuximab-combination chemotherapy as third-line treatment. These results suggest that the assessment of CTCs might provide with important prognostic information for such patients.

[486]

TÍTULO / TITLE: - Epigenetic modifications in cell lines of human astrocytoma differentially regulate expression of apoptotic genes.

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

REVISTA / JOURNAL: - Childs Nerv Syst. 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1007/s00381-013-2258-6](#)

AUTORES / AUTHORS: - Solis-Paredes M; Eguia-Aguilar P; Chico-Ponce de Leon F; Sadowinski-Pine S; Perezpena-Diazconti M; Arenas-Huertero F

INSTITUCIÓN / INSTITUTION: - Departamento de Patología, Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico.

RESUMEN / SUMMARY: - OBJECTS: Epigenetic alterations, known as epimutations, act by deregulating gene expression. These epimutations are reversible through the action of chromatin modifiers such as DNA methylation (DNA-met) and histone deacetylases (HDAC) inhibitors. The present study evaluated the effect of 5-azacitidine (5-aza) and sodium butyrate (NaBu) as inhibitors of DNA-met and HDAC, respectively, in the expression of genes involved in apoptosis. METHODS: D54-MG, U373-MG, and T98G cell lines were exposed to 8 mM of NaBu and 12 μM of 5-aza, as well as a combination of both, for 24 h. The expression of the Bcl-2, Bak-1, Bax, Caspase-3, and Caspase-9 genes was assessed by RT-PCR. RESULTS: They show that the Bcl-2, Caspase-3, and Caspase-9 genes were not expressed by the U373-MG and T98G lines, and that the D54-MG line did not express Bak-1. After treatment, however, these cell lines expressed all of the genes due to the effect of 5-aza on Bak-1 in D54-MG and Caspase-9 in T98G, which suggests repression by DNA-met. Meanwhile, Bcl-2, Caspase-3, and Caspase-9 were in the U373-MG and T98G lines expressed after NaBu treatment. The effect of 5-aza induced an increase in the expression of Bax and Bcl-2, while NaBu produced a similar effect on the Bak-1 and Bax genes. CONCLUSIONS: Results reveal that histone deacetylation is the principle mechanism for repressing these genes and that their basal expression is regulated primarily by this form of histone modification.

[487]

TÍTULO / TITLE: - Low-dose arsenic trioxide enhances 5-aminolevulinic acid-induced PpIX accumulation and efficacy of photodynamic therapy in human glioma.

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

REVISTA / JOURNAL: - J Photochem Photobiol B. 2013 Jun 26;127C:61-67. doi: 10.1016/j.jphotobiol.2013.06.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.jphotobiol.2013.06.001](#)

AUTORES / AUTHORS: - Wang C; Chen X; Wu J; Liu H; Ji Z; Shi H; Gao C; Han D; Wang L; Yang G; Fu C; Li H; Zhang D; Liu Z; Li X; Yin F; Zhao S

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, People's Republic of China; Institute of Brain Science, Harbin Medical University, Heilongjiang Province, People's Republic of China; The Chinese-German Center of Academic Excellence in Neuroscience, Harbin, Heilongjiang Province, People's Republic of China.

RESUMEN / SUMMARY: - Among glioma treatment strategies, 5-aminolevulinic acid (5-ALA)-based fluorescence-guided resection (FGR) and photodynamic therapy (PDT) have been used as effective novel approaches against malignant glioma. However, insufficient intracellular protoporphyrin IX (PpIX) accumulation limits the application of FGR and PDT in the marginal areas of gliomas. To overcome these issues, we assessed the intracellular levels of PpIX in human glioma cell lines and rat cortical astrocytes pretreated with 0.1µM arsenic trioxide (ATO). Apoptosis and cell viability after PDT were evaluated using Annexin V-FITC apoptosis detection kit and MTT assay, respectively. In order to find out the possible mechanism, we investigated the expression of the key enzymes in the heme biosynthesis pathway, which regulates porphyrin synthesis in glioma cells. Our findings showed that the 5-ALA-induced PpIX accumulation in glioma cell lines pretreated with 0.1µM ATO was increased relative to the control groups. No changes in fluorescence intensity were detected in the rat cortical astrocytes pretreated using the same ATO concentration. Apoptosis following PDT in glioma cells pretreated with 0.1µM ATO were significantly higher than in control groups, especially late apoptotic cells, while the cell viability was decreased. The expression of CPOX was upregulated in glioma cells after pretreatment with 0.1µM ATO. We concluded that ATO was a potential optional approach in enhancing intracellular PpIX accumulation and improving the benefits of 5-ALA-induced FGR and PDT in glioma.

[488]

TÍTULO / TITLE: - In vitro and in silico studies of MDM2/MDMX isoforms predict Nutlin-3^a sensitivity in well/de-differentiated liposarcomas.

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

REVISTA / JOURNAL: - Lab Invest. 2013 Sep 9. doi: 10.1038/labinvest.2013.107.

●● Enlace al texto completo (gratis o de pago) [1038/labinvest.2013.107](#)

AUTORES / AUTHORS: - Bozzi F; Conca E; Laurini E; Posocco P; Lo Sardo A; Jocolle G; Sanfilippo R; Gronchi A; Perrone F; Tamborini E; Pelosi G; Pierotti MA; Maestro R; Pricl S; Pilotti S

INSTITUCIÓN / INSTITUTION: - Laboratory of Experimental Molecular Pathology, Department of Pathology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy.

RESUMEN / SUMMARY: - The molecular marker of well-differentiated/de-differentiated liposarcomas is MDM2 gene amplification coupled with protein overexpression and

wild-type TP53. MDMX is a recently identified MDM2 homolog and its presence in this tumor is unexplored. Our aim was to investigate the role of full-length MDM2 and MDMX proteins and their isoforms in surgical specimens of well-differentiated/de-differentiated liposarcomas in view of Nutlin-3^a (a MDM2 inhibitor) treatment. Frozen and matched formalin-fixed, paraffin-embedded material from surgical specimens was examined by means of: (1) fluorescence in situ hybridization to determine MDM2 and MDMX gene copy numbers; (2) RT-PCR and densitometry to analyze alternative splicing forms of mdm2 and mdmx; (3) immunoblotting and immunohistochemistry to assess the corresponding translated proteins; and (4) in vitro and in silico assays to determine their affinity for Nutlin-3^a. All these cases showed MDM2 gene amplification with an MDMX disomic pattern. In all cases, the full-length mdm2 transcript was associated with the mdm2-b transcript, with ratios ranging from 0.07 to 5.6, and both were translated into protein; mdmx and mdmx-s were co-transcribed, with ratios ranging from 0.1 to 5.6. MDMX-S was frequently more upregulated than MDMX at both transcriptional and protein level. Each case showed different amounts of mdm2, mdm2-b, mdmx, and mdmx-s transcripts and the corresponding proteins. In vitro assays showed that Nutlin-3^a was ineffective against MDM2-B and was unable to disrupt the MDMX/TP53 and MSMX-S/TP53 complexes. Molecular simulations confirmed these in vitro findings by showing that MDM2 has high Nutlin-3^a affinity, followed by MDMX-S, MDMX, and MDM2-B. Nutlin-3^a is predicted to be a good therapeutic option for well-differentiated/de-differentiated liposarcomas. However, our findings predict heterogeneous responses depending on the relative expression of mdm2, mdm2-b, mdmx, and mdmx-s transcripts and proteins. Laboratory Investigation advance online publication, 9 September 2013; doi:10.1038/labinvest.2013.107.

[489]

TÍTULO / TITLE: - HER2/neu gene amplification determines the sensitivity of uterine serous carcinoma cell lines to AZD8055, a novel dual mTORC1/2 inhibitor.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Sep 4. pii: S0090-8258(13)01118-9. doi: 10.1016/j.ygyno.2013.08.033.

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

AUTORES / AUTHORS: - English DP; Roque DM; Carrara L; Lopez S; Bellone S; Cocco E; Bortolomai I; Schwartz PE; Rutherford T; Santin AD

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, 333 Cedar Street, PO Box 208063, New Haven, CT 06520-8063, USA.

RESUMEN / SUMMARY: - OBJECTIVE: To evaluate c-erbB2 gene amplification in a series of primary uterine serous carcinoma (USC) cell lines. To assess the efficacy of AZD8055, a novel dual mTORC1/2 inhibitor against primary HER2/neu amplified vs HER2/neu not

amplified USC cell lines. METHODS: Twenty-two primary USC cell lines were evaluated for c-erbB2 oncogene amplification by FISH assays. In vitro sensitivity to AZD8055 was evaluated by flow-cytometry-based viability and proliferation assays. Cell cycle profile and downstream cellular responses to AZD8055 were assessed by measuring the DNA content of cells and by phosphorylation of the S6 protein by flow-cytometry. RESULTS: Nine of 22 (40.9%) USC cell lines demonstrated c-erbB2 gene amplification by FISH. AZD8055 caused a strong differential growth inhibition in USC cell lines, with high HER-2/neu-expressors demonstrating significantly higher sensitivity when compared to low HER-2/neu-expressors (AZD-8055 IC50 mean \pm SEM=0.27 \pm 0.05 μ M in c-erbB2 amplified versus 1.67 \pm 0.68 μ M in c-erbB2 not amplified tumors, P=0.03). AZD8055 growth-inhibition was associated with a significant and dose-dependent increase in the percentage of cells blocked in the G0/G1 cell cycle phase and a dose-dependent decline in pS6 levels in both c-erbB2 amplified vs c-erbB2 not amplified USC cell lines. CONCLUSIONS: AZD8055 may represent a novel targeted therapeutic agent in patients harboring advanced/recurrent/refractory USC. c-erbB2 gene amplification may represent a biomarker to identify USC patients who may benefit most from the use of AZD8055.

[490]

TÍTULO / TITLE: - Second-Generation Tyrosine Kinase Inhibitors in First-Line Treatment of Chronic Myeloid Leukaemia (CML).

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

REVISTA / JOURNAL: - BioDrugs. 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1007/s40259-013-0056-z](#)

AUTORES / AUTHORS: - Abruzzese E; Breccia M; Latagliata R

INSTITUCIÓN / INSTITUTION: - Hematology, S. Eugenio Hospital, Tor Vergata University, P. le dell'Umanesimo 10, 00144, Rome, Italy, elisabetta.abruzzo@uniroma2.it.

RESUMEN / SUMMARY: - Tyrosine kinase inhibitors (TKIs) have contributed to marked improvements in survival in patients with chronic myeloid leukaemia (CML). This article discusses the place of the second-generation TKIs dasatinib and nilotinib in the first-line treatment of CML and is based on published literature. The new agents are more potent and effective than imatinib. Data from pivotal clinical trials indicate that response to dasatinib and nilotinib is greater and more rapid than that to imatinib, resulting in a higher probability of patients achieving an optimal response to treatment. Differences between the newer agents with respect to patient groups for whom caution is advised, drug interaction potential, haematological toxicity, pulmonary toxicity, changes in the immune system and effects on laboratory parameters are discussed. With similar levels of efficacy, the choice of second-generation agents should be guided by the characteristics of the individual patient and the most suitable dosing regimen.

[491]

TÍTULO / TITLE: - Phycion from marine-derived fungus *Microsporium* sp. induces apoptosis in human cervical carcinoma HeLa cells.

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

REVISTA / JOURNAL: - Microbiol Res. 2013 Sep 23. pii: S0944-5013(13)00141-9. doi: 10.1016/j.micres.2013.09.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.micres.2013.09.001](#)

AUTORES / AUTHORS: - Wijesekara I; Zhang C; Van Ta Q; Vo TS; Li YX; Kim SK

INSTITUCIÓN / INSTITUTION: - Marine Biochemistry & Molecular Biology Laboratory, Department of Chemistry, Pukyong National University, Busan 608-737, Republic of Korea; Marine Bioprocess Research Center, Pukyong National University, Busan 608-737, Republic of Korea.

RESUMEN / SUMMARY: - Recently, the relationship between apoptosis and cancer has been emphasized and the induction of apoptosis is recognized as one of the key mechanisms of anti-cancer agents. Marine-derived fungi are valuable sources of structurally diverse bioactive anticancer agents. In the present study, a marine-derived fungus, *Microsporium* sp. was cultured and an anthraquinone derivative, phycion (11.8mg) was isolated from the culture broth extract (1710mg). Phycion has shown cytotoxic effect on human cervical carcinoma HeLa cells and its apoptosis induction in HeLa cells was investigated by the expressions of p53, p21, Bax, Bcl-2, caspase-9, and caspase-3 proteins. The Western blot analysis has revealed that phycion could significantly induce cell apoptosis through down-regulating of Bcl-2 expression, up-regulating of Bax expression, and activating the caspase-3 pathway. Furthermore, phycion induced the formation of reactive oxygen species (ROS) in HeLa cells. Collectively, these results suggest that phycion could be a potential candidate in the field of anticancer drug discovery against human cervical cancer.

[492]

TÍTULO / TITLE: - FLAIR-Only Progression in Bevacizumab-Treated Relapsing Glioblastoma Does Not Predict Short Survival.

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

REVISTA / JOURNAL: - Oncology. 2013 Sep 5;85(3):191-195.

●● Enlace al texto completo (gratis o de pago) [1159/000354692](#)

AUTORES / AUTHORS: - Schaub C; Greschus S; Seifert M; Waha A; Blasius E; Rasch K; Landwehr C; Mack F; Schafer N; Kebir S; Vilz B; Scheffler B; Bostrom J; Simon M; Urbach H; Glas M; Herrlinger U

INSTITUCIÓN / INSTITUTION: - Division of Clinical Neurooncology, Department of Neurology, University of Bonn Medical Center, Bonn, Germany.

RESUMEN / SUMMARY: - Objectives: In this study, we analyzed the prognostic value of different MRI progression patterns for survival in patients with recurrent malignant glioma treated with the vascular endothelial growth factor antibody bevacizumab. Patients and Methods: Twenty-six adult patients with recurrent malignant glioma treated with bevacizumab or bevacizumab/irinotecan were retrospectively analyzed for the development of contrast-enhanced (T1-weighted MRI) and T2/FLAIR lesions. According to the progression pattern, patients were divided into 3 subgroups: (1) patients with primarily progressive contrast-enhanced lesions in the first MRI after initiation of therapy ('primary PD group'); (2) patients with stable or regressive enhanced lesions but progressive FLAIR lesions ('FLAIR-only PD group'), and (3) patients with stable or regressive contrast-enhanced T1 and FLAIR lesions ('no PD group'). Results: Overall survival (OS) in the 6 patients in the FLAIR-only PD group was not significantly different from the 11 patients in the no PD group (median 311 vs. 254 days, respectively). In contrast, survival in the FLAIR-only PD group was significantly better ($p = 0.025$) than in the primary PD group. Conclusion: FLAIR-only progression is not an independent prognostic factor negatively influencing OS in recurrent glioblastoma treated with bevacizumab and should not lead to discontinuation of bevacizumab therapy. © 2013 S. Karger AG, Basel.

[493]

TÍTULO / TITLE: - WITHDRAWN: Down-regulation of long non-coding RNA TUG1 suppresses melanoma cell proliferation and induces apoptosis via up-regulating microRNA-9.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 18. pii: S0006-291X(13)01521-0. doi: 10.1016/j.bbrc.2013.09.050.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.09.050

AUTORES / AUTHORS: - Liu Y; Yang S; Zhang X

INSTITUCIÓN / INSTITUTION: - Institute of Dermatology and Department of Dermatology at No.1 Hospital, Anhui Medical University, Hefei, Anhui, China; Department of Dermatology and Venereology, Anhui Medical University, Hefei, Anhui, China; State Key Laboratory Incubation Base of Dermatology, Ministry of National Science and Technology, Hefei, Anhui, China.

RESUMEN / SUMMARY: - This article has been withdrawn at the request of the author. The Publisher apologizes for any inconvenience this may cause. The full Elsevier Policy on Article Withdrawal can be found at elsevier.com/locate/withdrawalpolicy.

[494]

TÍTULO / TITLE: - Prognostic significance of extracellular matrix degrading enzymes-cathepsin L and matrix metalloproteases-2 [MMP-2] in human pancreatic cancer.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Aug;31(7):461-71. doi: 10.3109/07357907.2013.820318.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.820318](#)

AUTORES / AUTHORS: - Singh N; Das P; Datta Gupta S; Sahni P; Pandey RM; Gupta S; Chauhan SS; Saraya A

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology & Human Nutrition, All India Institute of Medical Sciences, New Delhi, India.

RESUMEN / SUMMARY: - In the present study, we assessed the expression of extracellular matrix (ECM) degrading proteases-cathepsin L and matrix metalloprotease-2 (MMP-2) in pancreatic cancer tissue and correlated their levels with clinicopathological parameters and survival. Both the proteases were expressed in the majority of the tumor tissues examined. Staining intensity of cathepsin L was significantly higher in the tumor stroma compared to tumor epithelium while MMP-2 staining showed no such difference. Both proteases showed correlation with some of the clinicopathological parameters but only cathepsin L expression in tumor epithelium predicted a poor prognosis for the disease.

[495]

TÍTULO / TITLE: - Anti-apoptotic phenotypes of cholestan-3beta,5alpha,6beta-triol-resistant human cholangiocytes: Characteristics contributing to the genesis of cholangiocarcinoma.

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

REVISTA / JOURNAL: - J Steroid Biochem Mol Biol. 2013 Aug 16;138C:368-375. doi: 10.1016/j.jsbmb.2013.08.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.jsbmb.2013.08.004](#)

AUTORES / AUTHORS: - Jusakul A; Loilome W; Namwat N; Techasen A; Kuver R; Ioannou GN; Savard C; Haigh WG; Yongvanit P

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; Liver Fluke and Cholangiocarcinoma Research Center, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA; Department of Veterans Affairs Medical Center, Seattle, WA, USA.

RESUMEN / SUMMARY: - The oxysterols cholestan-3beta,5alpha,6beta-triol (Triol) and 3-keto-cholest-4-ene (3K4) are increased in *Opisthorchis viverrini*-associated hamster cholangiocarcinoma and induce DNA damage and apoptosis via a mitochondria-dependent mechanism in MMNK-1 human cholangiocytes. Based on these observations, we hypothesized that chronic exposure of cholangiocytes to these

pathogenic oxysterols may allow a growth advantage to a subset of these cells through selection for resistance to apoptosis, thereby contributing to cholangiocarcinogenesis. To test this hypothesis, we cultured MMNK-1 cells long-term in the presence of Triol. Alteration in survival and apoptotic factors of Triol-exposed cells were examined. Cells cultured long-term in the presence of Triol were resistant to H₂O₂-induced apoptosis, and demonstrated an increase in the phosphorylation of p38-alpha, CREB, ERK1/2 and c-Jun. Elevations in the ratio of Bcl-2/Bax and in the protein levels of anti-apoptotic factors including cIAP2, clusterin, and survivin were detected. These results show that long-term exposure of MNNK-1 cells to low doses of Triol selects for kinase-signaling molecules which regulate resistance to apoptosis and thereby enhance cell survival. Clonal expansion of such apoptosis-resistant cells may contribute to the genesis of cholangiocarcinoma.

[496]

TÍTULO / TITLE: - Human BDH2, an anti-apoptosis factor, is a novel poor prognostic factor for de novo cytogenetically normal acute myeloid leukemia.

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

REVISTA / JOURNAL: - J Biomed Sci. 2013 Aug 14;20(1):58.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1423-0127-20-58](#)

AUTORES / AUTHORS: - Yang WC; Tsai WC; Lin PM; Yang MY; Liu YC; Chang CS; Yu WH; Lin SF

RESUMEN / SUMMARY: - BACKGROUND: The relevance of recurrent molecular abnormalities in cytogenetically normal (CN) acute myeloid leukemia (AML) was recently acknowledged by the inclusion of molecular markers such as NPM1, FLT3, and CEBPA as a complement to cytogenetic information within both the World Health Organization and the European Leukemia Net classifications. Mitochondrial metabolism is different in cancer and normal cells. A novel cytosolic type 2-hydroxybutyrate dehydrogenase, BDH2, originally named DHRS6, plays a physiological role in the cytosolic utilization of ketone bodies, which can subsequently enter mitochondria and the tricarboxylic acid cycle. Moreover, BDH2 catalyzes the production of 2, 3-DHBA during enterobactin biosynthesis and participates in 24p3 (LCN2)-mediated iron transport and apoptosis. RESULTS: We observed that BDH2 expression is an independent poor prognostic factor for CN-AML, with an anti-apoptotic role. Patients with high BDH2 expression have relatively shorter overall survival (P = 0.007) and a low complete response rate (P = 0.032). BDH2-knockdown (BDH2-KD) in THP1 and HL60 cells increased the apoptosis rate under reactive oxygen species stimulation. Decrease inducible survivin, a member of the inhibitors of apoptosis family, but not members of the Bcl-2 family, induced apoptosis via a caspase-3-independent pathway upon BDH2-KD. CONCLUSIONS: BDH2 is a novel

independent poor prognostic marker for CN-AML, with the role of anti-apoptosis, through surviving.

[497]

TÍTULO / TITLE: - MPT0B169, a New Tubulin Inhibitor, Inhibits Cell Growth and Induces G2/M Arrest in Nonresistant and Paclitaxel-Resistant Cancer Cells.

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

REVISTA / JOURNAL: - Pharmacology. 2013;92(1-2):90-8. doi: 10.1159/000351852. Epub 2013 Aug 16.

●● Enlace al texto completo (gratis o de pago) [1159/000351852](#)

AUTORES / AUTHORS: - Lee WH; Liu HE; Chang JY; Liou JP; Huang HM

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Taipei Medical University-Shuang Ho Hospital, Taipei, Taiwan.

RESUMEN / SUMMARY: - The polymerization of tubulin molecules forms microtubules which are considered an attractive target for cancer treatment. Herein, we synthesized a new tubulin inhibitor, MPT0B169 (2-dimethylamino-N-[1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1H-indol-7-yl]-acet amide) and demonstrated its action in leukemia cell lines HL60 and NB4 and lymphoma cell line U937. We found that MPT0B169 prevented tubulin assembly by binding the colchicine-binding site of tubulin in vitro. MPT0B169 also induced tubulin depolymerization in vivo. MPT0B169 inhibited the growth of HL60, NB4, and U937 cells in dose- and time-dependent manners. It also inhibited the growth of paclitaxel-resistant cancer cells. In addition, MPT0B169 caused G2/M cell cycle arrest in nonresistant and paclitaxel-resistant cancer cells, with a concomitant increase in cyclin B1 levels and cyclin-dependent kinase 1 (CDK1) phosphorylation. These results suggest that MPT0B169, a tubulin inhibitor, inhibits cell growth and induces G2/M cell cycle arrest of cancer cells through the disruption of tubulin polymerization.

[498]

TÍTULO / TITLE: - Pazopanib a tyrosine kinase inhibitor with strong anti-angiogenic activity: A new treatment for metastatic soft tissue sarcoma.

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

REVISTA / JOURNAL: - Crit Rev Oncol Hematol. 2013 Sep 4. pii: S1040-8428(13)00189-3. doi: 10.1016/j.critrevonc.2013.08.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.critrevonc.2013.08.012](#)

AUTORES / AUTHORS: - Ranieri G; Mammi M; Donato Di Paola E; Gallelli L; Citraro R; Gadaleta CD; Marech I; Ammendola M; De Sarro G

INSTITUCIÓN / INSTITUTION: - Interventional Radiology Unit with Integrated Section of Translational Medical Oncology, National Cancer Institute, Giovanni Paolo II, Bari, Italy. Electronic address: girovan@tiscalinet.it.

RESUMEN / SUMMARY: - Soft tissue sarcomas (STS) are rare tumors with mesenchymal origin, accounting for 1% of all human cancer. Local control of STS can be obtained through the use of surgery and radiotherapy. In about 40% of these patients, disease will recur at distant sites, and of these more than 90% will die because of this aggressive malignancy. In advanced and/or metastatic STS patients treated with anthracycline-based regimen the median overall survival is about 12 months, and it has remained unchanged during the last 20 years. Clearly, this strongly suggests the need for discover more active compounds in STS, such as imatinib in GIST or dermatofibrosarcoma patients. In this paper we describe the crucial role of angiogenesis mechanisms in sarcomas development and progression. Consequentially, we focus on pazopanib, a novel multitargeted tyrosine kinase inhibitor with anti-angiogenic activity, mainly due to VEGFR2 pathway interference. We also analyze principal completed trials leading pazopanib approval in sarcomas pretreated patients.

[499]

TÍTULO / TITLE: - EGFR-Inhibition Enhances Apoptosis in Irradiated Human Head and Neck Xenograft Tumors Independent of Effects on DNA Repair.

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

REVISTA / JOURNAL: - Radiat Res. 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [1667/RR3349.2](#)

AUTORES / AUTHORS: - Stegeman H; Span PN; Cockx SC; Peters JP; Rijken PF; van der Kogel AJ; Kaanders JH; Bussink J

INSTITUCIÓN / INSTITUTION: - a Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and.

RESUMEN / SUMMARY: - Epidermal growth factor receptor (EGFR) inhibition using cetuximab improves the efficacy of radiotherapy in only a subgroup of head and neck squamous cell carcinoma (HNSCC) patients. Therefore, to improve patient selection a better understanding of tumor characteristics that affect treatment is necessary. Here, we investigated the effect of cetuximab on repair of radiation-induced DNA damage in a HNSCC xenograft model, which shows a synergistic effect to cetuximab and radiotherapy (SCCNij185) and a HNSCC model, which shows no additive effect of cetuximab to radiotherapy (SCCNij153). In both tumor models, clear increases were seen in the number of 53BP1 and Rad51 foci after irradiation. 53BP1 foci were present at comparable levels in hypoxic and normoxic tumor areas of the tumor xenografts, while the number of Rad51 foci was significantly higher in normoxic areas compared to hypoxic areas ($P < 0.05$). In both SCCNij185 and SCCNij153 xenografts an increased number of 53BP1 foci was observed in tumors treated with cetuximab and

radiotherapy compared to radiotherapy alone. In SCCNij185 this increase was statistically significant in normoxic tumor areas ($P = 0.04$) and in SCCNij153 in both hypoxic and normoxic areas ($P = 0.007$ and $P = 0.02$, respectively). The number of Rad51 foci was not significantly different when cetuximab was added to radiotherapy compared to radiotherapy alone. Levels of pEGFR and pERK1/2 were decreased when cetuximab was added to radiotherapy in SCCNij185, but not in SCCNij153. Apoptosis was also only increased in SCCNij185 tumors at 4 days after cetuximab and radiotherapy treatment ($P < 0.01$). In conclusion, cetuximab inhibited DNA repair in both HNSCC models, but this effect was not predictive for the radiosensitizing effect of cetuximab in vivo. This lack of correlation may be related to differential effects of cetuximab and radiotherapy on ERK1/2 signaling and a decreased induction of apoptosis by cetuximab and radiotherapy in the resistant model.

[500]

TÍTULO / TITLE: - Outcomes of splenectomy versus cladribine for hairy cell leukemia in resource limited settings.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 4.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.839786](#)

AUTORES / AUTHORS: - Lad DP; Malhotra P; Khadwal A; Prakash G; Suri V; Kumari S; Jain S; Das R; Varma N; Varma S

[501]

TÍTULO / TITLE: - Glioma-derived galectin-1 regulates innate and adaptive antitumor immunity.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 9. doi: 10.1002/ijc.28426.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28426](#)

AUTORES / AUTHORS: - Verschuere T; Toelen J; Maes W; Poirier F; Boon L; Tousseyn T; Mathivet T; Gerhardt H; Mathieu V; Kiss R; Lefranc F; Van Gool SW; Vleeschouwer SD

INSTITUCIÓN / INSTITUTION: - Department of Neurosciences, Laboratory of Experimental Neurosurgery and Neuroanatomy, KU Leuven, Leuven, Belgium.

RESUMEN / SUMMARY: - Galectin-1 is a glycan-binding protein, which is involved in the aggressiveness of glioblastoma (GBM) in part by stimulating angiogenesis. In different cancer models, galectin-1 has also been demonstrated to play a pivotal role in tumor-mediated immune evasion especially by modulating cells of the adaptive immune system. It is yet unknown whether the absence or presence of galectin-1 within the glioma microenvironment also causes qualitative or quantitative differences in innate and/or adaptive antitumor immune responses. All experiments were performed in the

orthotopic GL261 mouse high-grade glioma model. Stable galectin-1 knockdown was achieved via transduction of parental GL261 tumor cells with a lentiviral vector encoding a galectin-1-targeting miRNA. We demonstrated that the absence of tumor-derived but not of host-derived galectin-1 significantly prolonged the survival of glioma-bearing mice as such and in combination with dendritic cell (DC)-based immunotherapy. Both flow cytometric and pathological analysis revealed that the silencing of glioma-derived galectin-1 significantly decreased the amount of brain-infiltrating macrophages and myeloid-derived suppressor cells (MDSC) in tumor-bearing mice. Additionally, we revealed a pro-angiogenic role for galectin-1 within the glioma microenvironment. The data provided in this study reveal a pivotal role for glioma-derived galectin-1 in the regulation of myeloid cell accumulation within the glioma microenvironment, the most abundant immune cell population in high-grade gliomas. Furthermore, the prolonged survival observed in untreated and DC-vaccinated glioma-bearing mice upon the silencing of tumor-derived galectin-1 strongly suggest that the in vivo targeting of tumor-derived galectin-1 might offer a promising and realistic adjuvant treatment modality in patients diagnosed with GBM.

[502]

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Aug 12. doi: 10.1002/ijc.28427.

●● [Enlace al texto completo \(gratis o de pago\) 1002/ijc.28427](#)

AUTORES / AUTHORS: - El Eit RM; Iskandarani AN; Saliba JL; Jabbour MN; Mahfouz RA; Bitar NM; Ayoubi HR; Zaatari GS; Mahon FX; De The HB; Bazarbachi AA; Nasr RR

INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Cell Biology and Physiology, American University of Beirut, Beirut, Lebanon.

RESUMEN / SUMMARY: - Imatinib is the standard of care in chronic myeloid leukemia (CML) therapy. However, imatinib is not curative since most patients who discontinue therapy relapse indicating that leukemia initiating cells (LIC) are resistant. Interferon alpha (IFN) induces hematologic and cytogenetic remissions and interestingly, improved outcome was reported with the combination of interferon and imatinib. Arsenic trioxide was suggested to decrease CML LIC. We investigated the effects of arsenic and IFN on human CML cell lines or primary cells and the bone marrow retroviral transduction/transplantation murine CML model. In vitro, the combination of arsenic and IFN inhibited proliferation and activated apoptosis. Importantly, arsenic and IFN synergistically reduced the clonogenic activity of primary bone marrow cells derived from CML patients. Finally, in vivo, combined interferon and arsenic treatment, but not single agents, prolonged the survival of primary CML mice. Importantly, the combination severely impaired engraftment into untreated secondary recipients, with some recipients never developing the disease, demonstrating a dramatic decrease in CML LIC activity. Arsenic/IFN effect on CML LIC activity was

significantly superior to that of imatinib. These results support further exploration of this combination, alone or with imatinib aiming at achieving CML eradication rather than long-term disease control.

[503]

TÍTULO / TITLE: - Phase I-II study of the farnesyl transferase inhibitor tipifarnib plus sequential weekly paclitaxel and doxorubicin-cyclophosphamide in HER2/neu-negative inflammatory carcinoma and non-inflammatory estrogen receptor-positive breast carcinoma.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Sep 26.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10549-013-2704-x](#)

AUTORES / AUTHORS: - Andreopoulou E; Vigoda IS; Valero V; Hershman DL; Raptis G; Vahdat LT; Han HS; Wright JJ; Pellegrino CM; Cristofanilli M; Alvarez RH; Fehn K; Fineberg S; Sparano JA

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Montefiore Medical Center-Weiler Division/ Albert Einstein College of Medicine, 2 South, 1825 Eastchester Road, Bronx, 10461, NY, USA.

RESUMEN / SUMMARY: - Tipifarnib (T) is a farnesyl transferase inhibitor (FTI) that enhances the antineoplastic effects of cytotoxic therapy in vitro, has activity in metastatic breast cancer, and enhances the pathologic complete response (pCR) rate to neoadjuvant doxorubicin-cyclophosphamide (AC) chemotherapy. We, therefore, performed a phase I-II trial of T plus neoadjuvant sequential weekly paclitaxel and 2-week AC chemotherapy in locally advanced breast cancer. Eligible patients with HER2-negative clinical stage IIB-IIIC breast cancer received 12 weekly doses of paclitaxel (80 mg/m²) followed by AC (60/600 mg/m² every 2 weeks and filgrastim), plus T (100 or 200 mg PO on days 1-3 of each P dose, and 200 mg PO on days 2-7 of each AC cycle). The trial was powered to detect an improvement in breast pCR rate from 15 to 35 % (alpha = 0.10, beta = 0.10) in two strata, including ER and/or PR-positive, non-inflammatory (stratum A) and inflammatory carcinoma (stratum B). Of the 60 patients accrued, there were no dose-limiting toxicities among the first six patients treated at the first T dose level (100 mg BID; N = 3) or second T dose level (200 mg BID; N = 3) plus paclitaxel. Breast pCR occurred in 6/33 patients (18 %, 95 % confidence intervals (CI) 7-36 %) and 1/22 patients (4 %, 95 % CI 0-8 %) in stratum B. Combination of the FTI T with weekly paclitaxel-AC is unlikely to be associated with a breast pCR rate of 35 % or higher in patients with locally advanced HER2/neu-negative inflammatory or non-inflammatory ER- and/or PR-positive breast carcinoma.

[504]

TÍTULO / TITLE: - Prognostic Impact of Positive Surgical Margins After Resection of Colorectal Cancer Liver Metastases: Reappraisal in the Era of Modern Chemotherapy.

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

REVISTA / JOURNAL: - World J Surg. 2013 Nov;37(11):2647-2654.

●● Enlace al texto completo (gratis o de pago) [1007/s00268-013-2186-3](#)

AUTORES / AUTHORS: - Tranchart H; Chirica M; Faron M; Balladur P; Lefevre LB; Svrcek M; de Gramont A; Tiret E; Paye F

INSTITUCIÓN / INSTITUTION: - Department of Digestive Surgery, Hopital Saint Antoine, 184 Rue du Faubourg Saint Antoine, 75012, Paris, France.

RESUMEN / SUMMARY: - BACKGROUND: The purpose of the present study was to assess the prognostic impact of positive surgical margins (R1) after liver resection (LR) of colorectal liver metastases (CRLM) in the era of modern chemotherapy regimens. R1 resection is a negative prognostic factor after LR of CRLM. The significance of R1 margins in the era of effective chemotherapy is unknown. METHODS: From January 2000 to December 2009, 215 patients (177 men: 62 %; median age 60 years; range 30-84 years) underwent LR of CRLM. The LR was considered R1 (margin <1 mm) in 49 patients (23 %) and R0 in 166 patients (77 %). Overall, 108 (50 %) patients received preoperative chemotherapy and 156 (72 %) patients received postoperative chemotherapy. RESULTS: With a median follow-up of 36 months (range 1-141 months), the 5-year overall survival (OS) rate (47 vs 40 %; p = 0.05) and the disease-free survival (DFS) rate (36 vs 23 %; p = 0.006) were significantly lower in the R1 group. Recurrence developed in 152 patients (71 %) and the rate of recurrence was significantly higher (84 vs 67 %; p = 0.02) in the R1 group. On multivariate analysis, N+ status of the colorectal primary tumor (p = 0.008), presence of radiologically occult disease (p = 0.04), and R1 resection (p = 0.03) were independent adverse predictors of OS. The N+ status of the primary tumor (p = 0.003) and R1 resection (p = 0.02) were independent adverse predictors of DFS. On multivariate analysis use of postoperative chemotherapy was the only independent predictor of improved DFS (p = 0.02) in the R1 group. CONCLUSIONS: A positive resection margin remains a significant poor prognostic factor after LR of CRLM in the era of modern chemotherapy. Postoperative chemotherapy reduces recurrence rates after R1 resection of CRLM.

[505]

TÍTULO / TITLE: - Peroxisome proliferator-activated receptor-alpha activation protects against endoplasmic reticulum stress-induced HepG2 cell apoptosis.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1826-0](#)

AUTORES / AUTHORS: - Tang WX; Wang LK; Wang YQ; Zong ZJ; Gao ZX; Liu XS; Shen YJ; Shen YX; Li YH

INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology, First Affiliated Hospital of Anhui Medical University, 288 Ji-xi Rd., Hefei, 230022, China.

RESUMEN / SUMMARY: - Live ischemia-reperfusion injury is associated with endoplasmic reticulum (ER) stress-induced apoptosis. Activation of peroxisome proliferator-activated receptor-alpha (PPARalpha) may inhibit hepatocyte apoptosis induced by oxidative stress and protect against liver injury. This study aimed to investigate the effects of PPARalpha activation, through a specific agonist, on ER stress-induced apoptosis in human liver hepatocellular carcinoma (HepG2) cells. HepG2 cells were challenged with H₂O₂ and treated with WY14643, a selective PPARalpha agonist, in the presence or absence of the PPARalpha antagonist of MK886. Cell viable assay (MTT) and immunostaining were used to evaluate cell viability. The level of apoptotic cell death was quantified through Annexin V/PI staining. Alanine aminotransferase, aspartate aminotransferase, and malondialdehyde levels were measured to determine the presence of cellular injury and oxidative stress. RT-PCR and Western blot analysis were used to detect mRNA and protein expression of PPARalpha, BiP, and CHOP. Immunofluorescence was utilized to determine the intracellular localization of CHOP. H₂O₂ and MK886 both reduced the viability of HepG2 cells, increased oxidative stress and apoptosis, up-regulated the BiP and CHOP expression, and induced CHOP translocation from the cytoplasm to the nucleus. Compared with cells treated with H₂O₂ alone, pre-administration of WY14643 increased cell viability, attenuated apoptosis, improved cell function, down-regulated BiP and CHOP expression and inhibited CHOP translocation. The effects of WY14643 were completely abolished using the MK886 antagonist. PPARalpha activation protects against H₂O₂-induced HepG2 cell apoptosis. The underlying mechanisms may be associated with its activation to suppress excessive ER stress.

[506]

TÍTULO / TITLE: - Afatinib, Erlotinib and Gefitinib in the First-Line Therapy of EGFR Mutation-Positive Lung Adenocarcinoma: A Review.

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

REVISTA / JOURNAL: - Onkologie. 2013;36(9):510-8. doi: 10.1159/000354627. Epub 2013 Aug 19.

●● Enlace al texto completo (gratis o de pago) [1159/000354627](#)

AUTORES / AUTHORS: - Kohler J; Schuler M

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Germany.

RESUMEN / SUMMARY: - Non-small cell lung cancer (NSCLC) consists of several histomorphologically defined phenotypes that display an enormous genetic variability. In recent years, epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma has emerged as a unique subset of NSCLC in terms of

etiopathogenesis and tumor biology. Since the introduction of the reversible EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib, patients with metastatic EGFR mutation-positive lung cancer can be offered a therapeutic alternative that has proven its superiority over standard platinum-based chemotherapy. However, primary or acquired resistance limits the therapeutic success of these targeted agents. Irreversible inhibitors targeting all ErbB family receptor tyrosine kinases, such as afatinib and dacomitinib, have been developed to confer sustained disease control in ErbB-dependent cancers. The large LUX-Lung 3 phase III trial recently reported afatinib to be clearly superior over the most effective platinum doublet in patients with EGFR mutation-positive lung cancer. To fully exploit the clinical activity of afatinib, proactive management of its gastrointestinal and dermatologic toxicities is advised. © 2013 S. Karger GmbH, Freiburg.

[507]

TÍTULO / TITLE: - Assessment of aggressiveness of rectal cancer using 3-T MRI: correlation between the apparent diffusion coefficient as a potential imaging biomarker and histologic prognostic factors.

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

REVISTA / JOURNAL: - Acta Radiol. 2013 Sep 4.

●● [Enlace al texto completo \(gratis o de pago\) 1177/0284185113503154](#)

AUTORES / AUTHORS: - Akashi M; Nakahusa Y; Yakabe T; Egashira Y; Koga Y; Sumi K; Noshiro H; Irie H; Tokunaga O; Miyazaki K

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Faculty of Medicine, Saga University, Saga, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Diffusion-weighted magnetic resonance imaging (DW-MRI) permits non-invasive assessment of tumor characteristics. PURPOSE: To assess the value of DW-MRI as a potential non-invasive marker of tumor aggressiveness in rectal cancer by analyzing the relationship between tumoral apparent diffusion coefficient (ADC) values of MRI and histopathologic prognostic parameters that are not affected by preoperative chemoradiation therapy. MATERIAL AND METHODS: Forty patients with rectal cancer were assessed with primary staging 3-T MRI, including DWI, before undergoing surgical therapy. In all patients, surgery was performed without neoadjuvant therapy. Mean tumor ADC was measured and compared between subgroups based on pretreatment carcinoembryonic antigen (CEA) levels, MRI parameters (e.g. postoperative local recurrence), and histopathologic parameters, including A (invasive distance: A1, T-stage; A2, mesorectal fascia [MRF] status), B (differentiation grade: B1, poorly differentiated; B2, moderately differentiated; B3, well differentiated), C (others: C1, N-stage; C2, lymphovascular invasion). RESULTS: Mean tumor ADCs were different when comparing groups stratified by histologic differentiation grades ($P = 0.0192$). There was no significant

difference in mean ADCs when stratifying patients according to CEA levels, T-stage, N-stage, MRF status, presence of lymphovascular invasion, or the presence of local recurrence. CONCLUSION: Significant correlations were found between mean ADC values and differentiation grade. ADC may be useful as an imaging biomarker of tumor aggressiveness, but it cannot serve as an independent biomarker of advanced rectal cancer.

[508]

TÍTULO / TITLE: - Effects of Fusaric Acid Treatment on HEP2 and Docetaxel-Resistant HEP2 Laryngeal Squamous Cell Carcinoma.

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

REVISTA / JOURNAL: - Chemotherapy. 2013 Sep 14;59(2):121-128.

●● Enlace al texto completo (gratis o de pago) [1159/000353718](#)

AUTORES / AUTHORS: - Ye J; Montero M; Stack Jr BC

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology-Head and Neck Surgery, University of Arkansas for Medical Sciences, Little Rock, Ark., USA.

RESUMEN / SUMMARY: - Background: Head and neck squamous cell carcinoma (HNSCC) can become resistant to some chemotherapy and becomes a clinical challenge when it recurs. There are few agents identified for second-line treatment of resistant head and neck cancer. Therefore, we evaluated the role of fusaric acid (FA) as a possible agent for treatment for chemotherapy-resistant laryngeal squamous cell carcinoma. Methods: The HEP2 and docetaxel-resistant HEP2 (HEP-Doc) cell lines were created from human laryngeal cancer. Cell lines were exposed to FA at increasing concentrations (0.1, 0.3, and 0.5 mM) and time intervals of 24, 48, 72, and 96 h. The effects on cell survival, apoptosis, and cytokine and protein expression were analyzed. Results: FA treatment in the HEP-Doc cells showed greater reduction of cell number and colony-forming units and more apoptosis when compared to HEP2 and required less time to reduce cell number. Four cytokines were detected in HEP2 cancer cells that increased with FA treatment. Pro-caspase-9 and -7 and poly (ADP-ribose) polymerase also increased with FA treatment. Conclusion: FA may be an agent to be considered in cases of HNSCC treatment resistance or post-docetaxel recurrence. Further investigation of FA in vitro and in vivo is indicated.

[509]

TÍTULO / TITLE: - Comparison of the Anti-Tumor Effects of Denosumab and Zoledronic Acid on the Neoplastic Stromal Cells of Giant Cell Tumor of Bone.

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

REVISTA / JOURNAL: - Connect Tissue Res. 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [3109/03008207.2013.848202](#)

AUTORES / AUTHORS: - Lau CP; Huang L; Chuen Wong K; Madhukar Kumta S

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics and Traumatology, The Chinese University of Hong Kong, Hong Kong, SAR, P.R. China.

RESUMEN / SUMMARY: - Abstract Denosumab and Zoledronic acid (ZOL) are two antiresorptive drugs currently in use for treating osteoporosis. They have different mechanisms of action but both have been shown to delay the onset of skeletal-related events in patients with giant cell tumor of bone (GCT). However, the anti-tumor mechanisms of denosumab on the neoplastic GCT stromal cells remain unknown. In this study, we focused on the direct effects of denosumab on the neoplastic GCT stromal cells and compared with ZOL. The microscopic view demonstrated a reduced cell growth in ZOL-treated but not in denosumab-treated GCT stromal cells. ZOL was found to exhibit a dose-dependent inhibition in cell growth in all GCT stromal cell lines tested and cause apoptosis in two out of three cell lines. In contrast, denosumab only exerted a minimal inhibitory effect in one cell line and did not induce any apoptosis. ZOL significantly inhibited the mRNA expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) in two GCT stromal cell lines whereas their protein levels remained unchanged. On the contrary, denosumab did not regulate RANKL and OPG expression at both mRNA and protein levels. Moreover, the protein expression of Macrophage Colony-Stimulating Factor (M-CSF), Alkaline Phosphatase (ALP), and Collagen alpha1 Type I were not regulated by denosumab and ZOL, either. Our findings provide new insights in the anti-tumor effect of denosumab on GCT stromal cells and raise a concern that tumor recurrence may occur after the withdrawal of the drug.

[510]

TÍTULO / TITLE: - Baseline and genotoxic compound induced gene expression profiles in HepG2 and HepaRG compared to primary human hepatocytes.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Oct;27(7):2031-2040. doi: 10.1016/j.tiv.2013.07.010. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.07.010](https://doi.org/10.1016/j.tiv.2013.07.010)

AUTORES / AUTHORS: - Jetten MJ; Kleinjans JC; Claessen SM; Chesne C; van Delft JH

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marlon.jetten@maastrichtuniversity.nl.

RESUMEN / SUMMARY: - Efforts are put into developing toxicogenomics-based toxicity testing methods using in vitro human cell models for improving human risk assessment/replacing animal models. Human in vitro liver models include HepG2, HepaRG and primary human hepatocytes (PHH). Studies on comparability/applicability of these cell types mainly focus on assessing baseline biotransformation

capacities/cytochrome P450-inducibility, but compound-induced gene expression profiles are at least as important. Therefore, we compared baseline and aflatoxin B1- and benzo(alpha)pyrene-induced gene expression profiles in HepG2, HepaRG and PHH (11-13 donors). At baseline, all liver models differ from each other with respect to whole genome gene expression levels. PHH show profound inter-individual differences, and are most similar to HepaRG. After compound exposure, induced gene expression profiles are more similar between cell models, especially for benzo(alpha)pyrene. Pathways involved in compound metabolism are induced in all 3 models, while others are more pronounced in a specific cell model. Examples are transcriptomic modifications of carbohydrate-related genes (HepaRG) and of receptor-related genes (PHH) after benzo(alpha)pyrene exposure, and of cell cycle-related genes (HepG2) after aflatoxin B1 exposure. PHH gene expression responses are the most heterogeneous. In conclusion, at base line level PHH are more similar to HepaRG than to HepG2, but for toxicogenomics applications both cell lines perform equally well in comparison to PHH.

[511]

TÍTULO / TITLE: - Cathepsin L silencing enhances arsenic trioxide mediated in vitro cytotoxicity and apoptosis in glioblastoma U87MG spheroids.

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

REVISTA / JOURNAL: - Exp Cell Res. 2013 Aug 19. pii: S0014-4827(13)00341-8. doi: 10.1016/j.yexcr.2013.08.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.yexcr.2013.08.011](#)

AUTORES / AUTHORS: - Primon M; Huszthy PC; Motaln H; Talasila KM; Torkar A; Bjerkvig R; Lah Turnsek T

INSTITUCIÓN / INSTITUTION: - Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana, Slovenia; Bia d.o.o., Ljubljana, Slovenia.

RESUMEN / SUMMARY: - Despite improved treatment options, glioblastoma multiforme (GBM) remains the most aggressive brain tumour with the shortest post-diagnostic survival. Arsenite (As₂O₃) is already being used in the treatment of acute promyelocytic leukaemia (APL), yet its effects on GBM have not been evaluated in detail. In U87MG cell monolayers, we have previously shown that arsenite cytotoxicity significantly increases upon transient inhibition of lysosomal protease Cathepsin L (CatL). As multicellular spheroids more closely represent in vivo tumours, we aimed to evaluate the impact of permanent CatL silencing on arsenite treatment in U87MG spheroids. CatL was stably silenced using shRNA expression plasmid packed lentiviruses. By using metabolic- and cell viability assays, we demonstrated that long-term CatL silencing significantly increased arsenite cytotoxicity in U87MG spheroids. Silenced CatL also increased arsenite-mediated apoptosis in spheroids via elevated p53 expression, Bax/Bcl2 ratio and caspase 3/7 activity, though with lower efficacy

than in monolayers. Arsenite cytotoxicity was enhanced by lower CatL activity, since similar cytotoxicity increase was also observed using the novel CatL inhibitor AT094. The results have significant translational impact, since stable CatL silencing would enable the application of lower systemic doses of arsenite to achieve the desired cytotoxic effects on GBMs in vivo.

[512]

TÍTULO / TITLE: - Nilotinib monotherapy induced complete remission in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to imatinib and dasatinib.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 11.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.842984](#)

AUTORES / AUTHORS: - Sekimizu M; Yamashita Y; Ueki H; Akita N; Hattori H; Maeda N; Horibe K

[513]

TÍTULO / TITLE: - Metabolism modifications and apoptosis induction after Cellfood™ administration to leukemia cell lines.

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

REVISTA / JOURNAL: - J Exp Clin Cancer Res. 2013 Sep 9;32(1):63.

●● Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-63](#)

AUTORES / AUTHORS: - Catalani S; Carbonaro V; Palma F; Arshakyan M; Galati R; Nuvoli B; Battistelli S; Canestrari F; Benedetti S

RESUMEN / SUMMARY: - BACKGROUND: Cellfood™ (CF) is a nutritional supplement containing deuterium sulphate, minerals, amino acids, and enzymes, with well documented antioxidant properties. Its organic and inorganic components are extracted from the red algae *Lithothamnion calcareum*, whose mineral extract has shown growth-inhibitory effect both on in vitro and in vivo models. The purpose of this study was to evaluate the antiproliferative effects of CF on leukemic cells. In fact, according to its capacity to modulate O₂ availability and to improve mitochondrial respiratory metabolism, we wondered if CF could affect cancer cell metabolism making cells susceptible to apoptosis. METHODS: Three leukemic cell lines, Jurkat, U937, and K562, were treated with CF 5 μl/ml up to 72 hours. Cell viability, apoptosis (i.e. caspase-3 activity and DNA fragmentation), hypoxia inducible factor 1 alpha (HIF-1α) concentration, glucose transporter 1 (GLUT-1) expression, lactate dehydrogenase (LDH) activity and lactate release in the culture medium were detected and compared with untreated cells. RESULTS: CF significantly inhibited leukemic cell viability by promoting cell apoptosis, as revealed by caspase-3 activation and DNA

laddering. In particular, CF treated cells showed lower HIF-1alpha levels and lower GLUT-1 expression as compared to untreated cells. At the same time, CF was able to reduce LDH activity and, consequently, the amount of lactate released in the extracellular environment. CONCLUSIONS: We supplied evidence for an antiproliferative effect of CF on leukemia cell lines by inducing cell death through an apoptotic mechanism and by altering cancer cell metabolism through HIF-1alpha and GLUT-1 regulation. Thanks to its antioxidative and proapoptotic properties, CF might be a good candidate for cancer prevention.

[514]

TÍTULO / TITLE: - Modified Cisplatin-based Transcatheter Arterial Chemoembolization for Large Hepatocellular Carcinoma: Multivariate Analysis of Predictive Factors for Tumor Response and Survival in a 163-patient Cohort.

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

REVISTA / JOURNAL: - J Vasc Interv Radiol. 2013 Aug 17. pii: S1051-0443(13)01132-9. doi: 10.1016/j.jvir.2013.06.017.

●● Enlace al texto completo (gratis o de pago) 1016/j.jvir.2013.06.017

AUTORES / AUTHORS: - Yoon HM; Kim JH; Kim EJ; Gwon DI; Ko GY; Ko HK

INSTITUCIÓN / INSTITUTION: - Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Poongnap-2dong, Songpa-gu, Seoul 138-736, Republic of Korea.

RESUMEN / SUMMARY: - PURPOSE: To evaluate the safety and efficacy of modified cisplatin-based transcatheter arterial chemoembolization for inoperable hepatocellular carcinomas (HCCs) larger than 5 cm in diameter, and the factors associated with tumor response and survival. MATERIALS AND METHODS: From January 2007 to November 2009, 163 patients who underwent modified cisplatin-based chemoembolization for inoperable large HCCs were evaluated. Predominant tumors were as large as 25 cm (median, 8.6 cm). Seventy-nine patients had a solitary tumor, and 84 had two or more tumors. Tumor response was evaluated per modified Response Evaluation Criteria In Solid Tumors. RESULTS: After chemoembolization, 65% of patients showed a tumor response. On multivariate analysis, tumor size ($P < .001$) and portal vein (PV) invasion ($P = .017$) were significant factors for tumor response. After chemoembolization, 97% of patients (56 of 58) with PV invasion received additional radiation therapy for PV tumor thrombosis. Median survival time was 15.8 months. On multivariate analysis, Child-Pugh class ($P = .001$), surgical resection ($P = .003$) or radiofrequency (RF) ablation ($P = .018$) after chemoembolization, and tumor response ($P = .002$) were significant factors for patient survival after chemoembolization. Major complications ($N = 5$) included acute renal failure ($n = 3$), cholecystitis with hepatic abscess ($n = 1$), and intractable pleural effusion ($n = 1$). CONCLUSIONS: Transcatheter arterial chemoembolization is safe and effective for large HCCs. Tumor size and PV invasion are

significant predictors of tumor response and, Child-Pugh class A disease, surgical resection after chemoembolization, RF ablation after chemoembolization, and tumor response are good prognostic factors for survival.

[515]

TÍTULO / TITLE: - A novel antibody-like TCRgammadelta-Ig fusion protein exhibits antitumor activity against human ovarian carcinoma.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Aug 3. pii: S0304-3835(13)00556-9. doi: 10.1016/j.canlet.2013.07.036.

●● Enlace al texto completo (gratis o de pago) 1016/j.canlet.2013.07.036

AUTORES / AUTHORS: - Zheng J; Guo Y; Ji X; Cui L; He W

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, National Key Laboratory of Medical Molecular Biology, Beijing, China. Electronic address: jingzheng0420@gmail.com.

RESUMEN / SUMMARY: - TCRgamma9delta2(OT3) is a tumor-specific TCR with a unique complementarity-determining region 3 (CDR3) sequence, referred to as OT3, in its delta2 chain. This region was identified in tumor-infiltrating lymphocytes (TILs) from human ovarian epithelial carcinoma. We demonstrated that TCRgamma9delta2(OT3)-Fc, a fusion protein composed of the complete extracellular domains of the gamma9 and delta2 chains linked to the Fc domains of human IgG1, exhibited successful binding to multiple human carcinoma cell lines. In vitro, TCRgamma9delta2(OT3)-Fc mediated cell killing via antibody-dependent cellular cytotoxicity (ADCC) in a dose-dependent manner. In vivo, TCRgamma9delta2(OT3)-Fc significantly inhibited tumor growth and enhanced survival in human ovarian carcinoma xenograft models. Our findings suggest that the TCRgamma9delta2(OT3)-Fc fusion protein possesses both the antigen-recognition properties of TCR gammadelta and the Fc-mediated effector functions of the antibody.

[516]

TÍTULO / TITLE: - INDUCTION BUT NOT INHIBITION OF COX-2 CONFERS HUMAN LUNG CANCER CELL APOPTOSIS BY CELECOXIB.

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

REVISTA / JOURNAL: - J Lipid Res. 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) 1194/jlr.M042283

AUTORES / AUTHORS: - Ramer R; Walther U; Borchert P; Laufer S; Linnebacher M; Hinz B

INSTITUCIÓN / INSTITUTION: - University of Rostock, Germany;

RESUMEN / SUMMARY: - The antitumorigenic mechanism of the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib is still a matter of debate. Among different structurally related COX-2 inhibitors, only celecoxib was found to cause apoptosis and cell death of human lung cancer cells (IC50 values of 19.96 μ M [A549], 12.48 μ M [H460] and 41.39 μ M [H358]) that was paralleled by a time- and concentration-dependent upregulation of COX-2 and peroxisome proliferator activated receptor gamma (PPARgamma) at mRNA and protein levels. Apoptotic death of celecoxib-treated cancer cells was suppressed by the PPARgamma antagonist GW-9662 and by siRNA targeting PPARgamma, and surprisingly also by the selective COX-2 inhibitor NS-398 and siRNA targeting COX-2. NS-398 (1 μ M) was shown to suppress celecoxib-induced COX-2 activity. Among the COX-2-dependent prostaglandins (PGs) induced upon celecoxib treatment, PGD2 and 15-deoxy-Delta12,14-PGJ2 were found to induce a cytosol-to-nucleus translocation of PPARgamma as well as a PPARgamma-dependent apoptosis. Celecoxib-elicited PPARgamma translocation was inhibited by NS-398. Finally, a COX-2- and PPARgamma-dependent cytotoxic action of celecoxib was also proven for primary human lung tumor cells. Together, our data demonstrate a proapoptotic mechanism of celecoxib involving initial upregulation of COX-2 and PPARgamma and a subsequent nuclear translocation of PPARgamma by COX-2-dependent PGs.

[517]

TÍTULO / TITLE: - Imatinib induces demethylation of miR-203 gene: An epigenetic mechanism of anti-tumor effect of imatinib.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Oct;37(10):1278-86. doi: 10.1016/j.leukres.2013.07.019. Epub 2013 Aug 13.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.leukres.2013.07.019](#)

AUTORES / AUTHORS: - Shibuta T; Honda E; Shiotsu H; Tanaka Y; Vellasamy S; Shiratsuchi M; Umemura T

INSTITUCIÓN / INSTITUTION: - Department of Health Sciences, Faculty of Medical Sciences, Graduate School of Medical Sciences, Kyushu University, Japan.

RESUMEN / SUMMARY: - MicroRNA (miRNA) is an important regulator of cellular proliferation, differentiation and death. Leukemia-specific signature of miRNAs suggests that epigenetic dysregulation of miRNAs is important for leukemogenesis. We focused on the role of DNA methylation of miR-203 which targets BCR-ABL1 mRNA. The microarray analysis showed that 48 miRNAs of CpG-rich 212 miRNAs were upregulated over 2-fold after imatinib treatment. Imatinib induced the demethylation of the miR-203 promoter region, resulting in low expression of targeted BCR-ABL1 gene, and loss of proliferation of leukemic cells. In conclusion, demethylation of miR-

203 is one of the molecular mechanisms of imatinib-induced inhibition of BCR-ABL1-positive leukemic cells.

[518]

TÍTULO / TITLE: - Cetuximab inhibits oral squamous cell carcinoma invasion and metastasis via degradation of epidermal growth factor receptor.

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

REVISTA / JOURNAL: - J Oral Pathol Med. 2013 Sep 11. doi: 10.1111/jop.12116.

●● Enlace al texto completo (gratis o de pago) [1111/jop.12116](#)

AUTORES / AUTHORS: - Dai W; Li Y; Zhou Q; Xu Z; Sun C; Tan X; Lu L

INSTITUCIÓN / INSTITUTION: - Department of Oromaxillofacial-Head and Neck Surgery, School of Stomatology, China Medical University, Shenyang, Liaoning, China.

RESUMEN / SUMMARY: - Cetuximab (Erbix, C225) is a chimeric monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR), inhibiting tumor growth, invasion, angiogenesis and metastasis. However, the mechanisms underlying the effect of Cetuximab in human oral squamous cell carcinoma (OSCC) remain unclear. Here, we report that Cetuximab modulates EGFR protein stability through the ubiquitin/proteasome pathway, resulting in the inhibition of human OSCC growth. Cetuximab significantly inhibited the migration and invasion of human OSCC cells by blocking epithelial/mesenchymal transition (EMT) and the AKT and ERK pathways. Furthermore, Cetuximab-inhibited cell growth by modulating the expression of integrin beta5. Taken together, these results provide novel insights into the mechanism of Cetuximab action and suggest potential therapeutic strategies for OSCC.

[519]

TÍTULO / TITLE: - A novel drug delivery system of intraperitoneal chemotherapy for peritoneal carcinomatosis using gelatin microspheres incorporating cisplatin.

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

REVISTA / JOURNAL: - Surgery. 2013 Sep 2. pii: S0039-6060(13)00201-8. doi: 10.1016/j.surg.2013.04.054.

●● Enlace al texto completo (gratis o de pago) [1016/j.surg.2013.04.054](#)

AUTORES / AUTHORS: - Gunji S; Obama K; Matsui M; Tabata Y; Sakai Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan. Electronic address: shutaro@kuhp.kyoto-u.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: Peritoneal carcinomatosis is a poor prognostic factor for patients with gastrointestinal, gynecologic, and pancreatic cancer. Cisplatin (CDDP) is among the most effective anti-cancer agents, although its adverse effects remain unresolved. For the treatment of peritoneal carcinomatosis with high-dose

CDDP, it is necessary to design a new delivery system of CDDP that can decrease systemic toxicity and achieve a better targeted, high-dose chemotherapy. **METHODS:** Microspheres were prepared from gelatin of a nontoxic, biodegradable material for the sustained release of CDDP. The gelatin microspheres incorporating CDDP (GM-CDDP) were injected intraperitoneally into a mouse model of peritoneal carcinomatosis; their therapeutic efficacy and adverse effects were evaluated in comparison with intraperitoneal administration of free CDDP. **RESULTS:** GM-CDDP released CDDP in the peritoneal cavity as a result of gelatin biodegradation. Mice treated with microspheres in the peritoneal cavity lived longer than mice treated with free CDDP (74 +/- 23 vs 40 +/- 23 days; P < .05). The mice treated with GM-CDDP also lost no weight, whereas the free CDDP group lost approximately 20% body weight (106 +/- 5% vs 80 +/- 7%; P < .001; body weight on day 1 = 100%). GM-CDDP significantly decreased the nephrotoxicity and hematotoxicity of CDDP. **CONCLUSION:** GM decreased the adverse effects of CDDP and allowed high-dose intraperitoneal chemotherapy with the control of CDDP. This technique of gradual local release may allow us to provide a high-dose, targeted, intraperitoneal chemotherapy with CDDP, resulting in enhanced anti-cancer effects. These gelatin microspheres may be useful as a drug carrier for the treatment of peritoneal carcinomatosis.

[520]

TÍTULO / TITLE: - High-dose methotrexate, high-dose cytarabine and temozolomide for the treatment of primary central nervous system lymphoma (PCNSL).

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):690. doi: 10.1007/s12032-013-0690-9. Epub 2013 Aug 20.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12032-013-0690-9](#)

AUTORES / AUTHORS: - Salamoon M; Hussein T; Kenj M; Bachour M

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Medical Oncology, Al Bairouni University Hospital, Damascus University, Damascus, Syria, maheroncology@yahoo.com.

RESUMEN / SUMMARY: - Treatment of primary central nervous system lymphoma (PCNSL) associates with low response rates and poor survival using conventional radio and chemotherapy. Due to its favorable toxicity profile, temozolomide has emerged as a new option for treatment of PCNSL in young patients. In this study, we report a series of PCNSL patients treated with an innovative regimen combining high dose of both cytarabine and methotrexate with temozolomide without radiotherapy or intrathecal chemotherapy. To evaluate a new intensive chemotherapy with temozolomide, trying to assess response and progression-free survival rates and if the results are promising, we are aiming at evaluating the overall survival (OS) taking into consideration the toxicity profile. The study was performed at Al Mowassa Charity

Hospital in Damascus (Syria). Forty patients with histologically confirmed PCNSL median age 52 years (range 20-65) years were included. Biopsies were cultured, and a karyotyping was made in 32 patients. An induction chemotherapy was started, and methotrexate 3 gr/m(2) over 12 h on day 1, cytarabine 3 gr/m(2) every 12 h on day 1 and temozolomide 150 mg/m(2) from day 2 through day 6 with a total of 6 cycles were given on a monthly basis. Among the 40 patients included in the study, a complete response was observed in 34 patients (85 %) and a partial response in the remaining 6 patients (15 %). Disease progressed in 8 out of 40 patients (20 %) while 32 patients are still living at 5 years making the OS reaching 77 %. Grade II nephrotoxicity was observed in 2 patients while grade III and IV hematotoxicity was observed in 5 patients. High dose of both Ara-C and MTX combined with temozolomide appears to be a good choice in the treatment of PCNSL, in the light of good response and OS rates, taking into consideration the acceptable toxicity profile. However, a larger trial is needed to make it an acceptable new combination as a first line for PCNSL patients.

[521]

TÍTULO / TITLE: - Molecular determinants of cancer cell sensitivity and resistance towards the sesquiterpene farnesol.

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

REVISTA / JOURNAL: - Pharmazie. 2013 Jul;68(7):608-15.

AUTORES / AUTHORS: - Kuete V; Efferth T

INSTITUCIÓN / INSTITUTION: - Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany.

[522]

TÍTULO / TITLE: - BTG1 inhibits breast cancer cell growth through induction of cell cycle arrest and apoptosis.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2137-44. doi: 10.3892/or.2013.2697. Epub 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2697](#)

AUTORES / AUTHORS: - Zhu R; Zou ST; Wan JM; Li W; Li XL; Zhu W

INSTITUCIÓN / INSTITUTION: - School of Radiation Medicine and Protection, Medical College, Soochow University, Suzhou, Jiangsu 215123, P.R. China.

RESUMEN / SUMMARY: - BTG1, which belongs to the BTG/Tob family, regulates cell cycle progression in a variety of cell types and appears to play roles in inhibiting proliferation, promoting apoptosis and stimulating cellular differentiation in multiple cell types. However, it remains unclear whether BTG1 is a breast cancer suppressor gene, and the role of BTG1 in breast cancer cell growth has not yet been determined.

In the present study, we observed that BTG1 was weakly expressed in human breast tumors and in breast cancer cells (MCF-7 and MDA-MB-231). In addition, we investigated the potential effects of BTG1 on breast cancer cell proliferation, cell cycle distribution and apoptosis after stable transfection with the BTG1 expression vector. We found that overexpression of BTG1 inhibited cell proliferation, induced G0/G1 cell cycle arrest and promoted apoptosis. Further investigation indicated that overexpression of BTG1 was involved in the inhibition of the expression of cell cycle-related proteins, cyclin B1 and cyclin D1, and pro-apoptotic factors, Bax and caspase-3, and was also involved in the promotion of anti-apoptotic factor Bcl-2. In vivo, animal experiments showed that tumors overexpressing BTG1 displayed a slower growth rate than the control xenografts. TUNEL end staining assay revealed that BTG1 induced tumor necrosis and apoptosis. Taken together, our data revealed that, in breast cancer cells, BTG1 inhibits cell growth through induction of cell cycle arrest and apoptosis. These results indicate that BTG1 may be used as a novel therapeutic target for human breast cancer treatment.

[523]

TÍTULO / TITLE: - Ursolic acid promotes colorectal cancer cell apoptosis and inhibits cell proliferation via modulation of multiple signaling pathways.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1235-43. doi: 10.3892/ijo.2013.2040. Epub 2013 Jul 26.

●● Enlace al texto completo (gratuito o de pago) [3892/ijo.2013.2040](#)

AUTORES / AUTHORS: - Lin J; Chen Y; Wei L; Shen A; Sferra TJ; Hong Z; Peng J

INSTITUCIÓN / INSTITUTION: - Academy of Integrative Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian 350122, P.R. China.

RESUMEN / SUMMARY: - The development of colorectal cancer (CRC) is strongly correlated with the aberrant activation of multiple intracellular signaling transduction cascades including STAT3, ERK, JNK and p38 pathways which usually function redundantly. In addition, crosstalk between these pathways forms a complicated signaling network that is regulated by compensatory mechanisms. Therefore, most of the currently used and single-target-based antitumor agents might not always be therapeutically effective. Moreover, long-term use of these agents often generates drug resistance. These problems highlight the urgent need for the development of novel anticancer chemotherapies. Ursolic acid (UA) is a major active compound present in many medicinal herbs that have long been used for the clinical treatment of CRC. Although previous studies have demonstrated an antitumor effect for UA, the precise mechanisms of its tumoricidal activity are not well understood. In the present study, using CRC mouse xenograft model and the HT-29 human colon carcinoma cell line, we evaluated the efficacy of UA against tumor growth in vivo and in vitro and

investigated the underlying molecular mechanisms. We found that UA inhibits cancer growth without apparent toxicity. Furthermore, UA significantly suppresses the activation of several CRC-related signaling pathways and alters the expression of critical target genes. These molecular effects lead to the induction of apoptosis and inhibition of cellular proliferation. These data demonstrate that UA possesses a broad range of anticancer activities due to its ability to affect multiple intracellular targets, suggesting that UA could be a novel multipotent therapeutic agent for cancer treatment.

[524]

TÍTULO / TITLE: - Serum C-reactive protein: a prognostic factor in metastatic urothelial cancer of the bladder.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):705. doi: 10.1007/s12032-013-0705-6. Epub 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0705-6](#)

AUTORES / AUTHORS: - Eggers H; Seidel C; Schrader AJ; Lehmann R; Wegener G; Kuczyk MA; Steffens S

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, eggers.hendrik@mh-hannover.de.

RESUMEN / SUMMARY: - Until today, there is no reliable prognostic or predictive parameter for the prognosis of patients with metastatic urothelial cancer of the bladder prior to chemotherapy. Recently, serum C-reactive protein (CRP) level has been shown to be associated with survival of patients with various malignancies including localized and metastatic renal cell carcinoma, upper urinary tract as well as penile cancer. The aim of this study was to evaluate the prognostic impact of the pretreatment CRP serum level in patients with metastatic urothelial cancer of the bladder. We retrospectively evaluated 34 patients with metastatic urothelial cancer of the bladder and information about the CRP level prior to chemotherapy. The CRP level was correlated with patient- and tumor-specific characteristics. Kaplan-Meier and log-rank analyses were employed to calculate progression-free (PFS) and overall survival (OS). Receiver operating characteristics (ROC) analysis was used to determine an optimal prognostic CRP cutoff value to predict cancer-specific death. The median PFS to first-line chemotherapy and the OS for the whole cohort were 3.3 and 24.3 months, respectively. Serum CRP in mg/l was significantly associated with patients' survival (HR 1.02, $p < 0.001$, univariate Cox-regression). ROC analysis identified a CRP value of 80 mg/l to be the optimal cutoff. The median PFS was 4.5 and 3.0 months ($p = 0.08$; Mann-Whitney test), and the calculated 1-year OS was 82.6 and 22.2 % for patients with a CRP < 80 and ≥ 80 mg/l, respectively (log-rank, $p < 0.001$). In contrast, neither

T-stage, tumor grade, sex, age nor the body mass index was related to the CRP level or associated with overall survival. This is the first analysis revealing that the CRP value prior to systemic treatment might be of prognostic significance and could enable better risk stratification for patients with metastatic urothelial cancer of the bladder.

[525]

TÍTULO / TITLE: - Cell surface markers for T and B lymphocytes activation and adhesion as putative prognostic biomarkers for head and neck squamous cell carcinoma.

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

REVISTA / JOURNAL: - Hum Immunol. 2013 Aug 28. pii: S0198-8859(13)00497-7. doi: 10.1016/j.humimm.2013.08.272.

●● Enlace al texto completo (gratis o de pago) 1016/j.humimm.2013.08.272

AUTORES / AUTHORS: - Andrade MC; Ferreira SB; Goncalves LC; De-Paula AM; de Faria ES; Teixeira-Carvalho A; Martins-Filho OA

INSTITUCIÓN / INSTITUTION: - Universidade Estadual de Montes Claros (UNIMONTES), 39401-089 Montes Claros, MG, Brazil. Electronic address: marileia@cpqrr.fiocruz.br.

RESUMEN / SUMMARY: - The study population comprised HNSCC patients, risk-positive controls (tobacco and alcoholism habits), and risk-negative controls (without risk factors). Significant increases in the activation status of CD4+ and CD8+ T-cells, and higher migration potentials of lymphocytes were observed in HNSCC patients compared with control groups. Although decreased frequency of CD19+ B lymphocytes was observed in HNSCC patients, a higher percentage of HLA-DR+ CD19+ B lymphocytes was detected in these individuals as compared with other evaluated groups. Metastasis and tumor grading were the major pathological parameters associated with significant alterations in the expression of activation molecules on circulating CD4+ and CD8+ T-cells. A reduced frequency of CD38-expressing CD8+ T-cells was the most relevant biomarker associated with HNSCC aggressiveness. Performance analysis suggested a cut-off point for the CD8+ CD38+ / CD8+ T-cell ratio of 7.0 for segregating patients according to tumor grading. In contrast, a higher proportion of CD8+ CD54+ / CD8+ T-cells could represent a relevant biomarker associated with metastasis in HNSCC patients, and performance analysis suggested a cut-off point for the CD8+ CD54+ / CD8+ T-cell ratio of 30 for segregating patients according to absence or presence of metastasis. The results obtained can increment immunological aspects of HNSCC and provide tools for the determination of cut-off scores of clinically relevant immunophenotypic prognostic biomarkers.

[526]

TÍTULO / TITLE: - Folate Receptor alpha Associated With Triple-Negative Breast Cancer and Poor Prognosis.

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

REVISTA / JOURNAL: - Arch Pathol Lab Med. 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) [5858/arpa.2013-0309-OA](#)

AUTORES / AUTHORS: - Zhang Z; Wang J; Tacha DE; Li P; Bremer RE; Chen H; Wei B; Xiao X; Da J; Skinner K; Hicks DG; Bu H; Tang P

INSTITUCIÓN / INSTITUTION: - From the Department of Pathology, West China Hospital, Sichuan University, Chengdu, China (Drs Zhang, Chen, Wei, and Bu);

RESUMEN / SUMMARY: - Context.-Folate receptor alpha (FRA) has been shown to be selectively expressed in several types of human cancer, including breast cancer. Currently, several FRA target therapies are under intensive study. Objective.-To investigate the expression pattern of FRA in a large cohort of patients with breast cancer and analyze its relationship with different clinicopathologic features, with expression of several key biomarkers, and with clinical outcome. Design.-Four hundred forty-seven cases of infiltrating ductal carcinoma diagnosed between 1997 and 2008 in our institution were identified and reviewed, and 25 blocks of tissue microassays were constructed. The association between expression of FRA and clinicopathologic features; expression of estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and Ki-67; and clinical outcome of these tumors were evaluated. Results.-The expression of FRA was significantly associated with tumors with high histologic grade, higher nodal stages, ER/PR negativity, and high proliferative activity (Ki-67 \geq 15%), and was independent of HER2/neu overexpression. In all, 74% of ER/PR-negative and 80% of triple-negative breast cancers expressed FRA. The expression of FRA was significantly associated with a worse disease-free survival. Conclusions.-Our data demonstrate that a significant subgroup of ER/PR-negative and triple-negative breast cancers expresses FRA, and its expression is associated with worse clinical outcome.

[527]

TÍTULO / TITLE: - Targeting PKCepsilon by miR-143 regulates cell apoptosis in lung cancer.

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

REVISTA / JOURNAL: - FEBS Lett. 2013 Sep 23. pii: S0014-5793(13)00712-6. doi: 10.1016/j.febslet.2013.09.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.febslet.2013.09.018](#)

AUTORES / AUTHORS: - Zhang N; Su Y; Xu L

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

RESUMEN / SUMMARY: - Non-small cell lung cancer (NSCLC) is one of the most common causes for lung cancer and cancer-related death. The imbalance between cell proliferation and apoptosis was suggested to play an important role in cancer

pathogenesis and PKCepsilon is one of the widely recognized targets. Here, we demonstrate that miR-143 is aberrantly downregulated in NSCLC tissue and negatively correlates with expression of PKCepsilon. We show that miR-143 specifically targets the 3'-UTR of PKCepsilon and regulates its expression. Treatment with miR-143 inhibitor mimics cell proliferation and apoptosis imbalance in NSCLC, while inhibition of PKCepsilon can reverse it. Our findings suggest that targeting PKCepsilon overexpression in NSCLC should be beneficial for lung cancer therapy.

[528]

TÍTULO / TITLE: - Novel synthetic curcumin analogues EF31 and UBS109 are potent DNA hypomethylating agents in pancreatic cancer.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Aug 7. pii: S0304-3835(13)00575-2. doi: 10.1016/j.canlet.2013.08.002.

●● Enlace al texto completo (gratis o de pago) 1016/j.canlet.2013.08.002

AUTORES / AUTHORS: - Nagaraju GP; Zhu S; Wen J; Farris AB; Adsay VN; Diaz R; Snyder JP; Mamoru S; El-Rayes BF

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, United States.

RESUMEN / SUMMARY: - DNA methylation is a rational therapeutic target in pancreatic cancer. The activity of novel curcumin analogues EF31 and UBS109 as demethylating agents were investigated. MiaPaCa-2 and PANC-1 cells were treated with vehicle, curcumin, EF31 or UBS109. EF31 and UBS109 resulted in significantly higher inhibition of proliferation and cytosine methylation than curcumin. Demethylation was associated with re-expression of silenced p16, SPARC, and E-cadherin. EF31 and UBS109 inhibited HSP-90 and NF-kappaB leading to downregulation of DNA methyltransferase-1 (DNMT-1) expression. Transfection experiments confirmed this mechanism of action. Similar results were observed in vitro when subcutaneous tumors (MiaPaCa-2) were treated with EF31 and UBS109.

[529]

TÍTULO / TITLE: - Potentiation of anticancer effect of valproic acid, an antiepileptic agent with histone deacetylase inhibitory activity, by the cyclin-dependent kinase inhibitor P276-00 in human non-small-cell lung cancer cell lines.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Sep 3. pii: S0169-5002(13)00365-6. doi: 10.1016/j.lungcan.2013.08.010.

●● Enlace al texto completo (gratis o de pago) 1016/j.lungcan.2013.08.010

AUTORES / AUTHORS: - Shirsath N; Rathos M; Chaudhari U; Sivaramakrishnan H; Joshi K

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Piramal Life Sciences, Piramal Enterprises Limited, 1 Nirlon Complex, Goregaon (East), Mumbai, Maharashtra 400 063, India.

RESUMEN / SUMMARY: - BACKGROUND: P276-00 is a novel cyclin-dependent kinase (CDK) inhibitor is in Phase II clinical trials. Valproic acid (VPA), an antiepileptic agent has been associated with anticancer activity, through the inhibition of histone deacetylase I. Here we investigate the effect of the combination of VPA and P276-00, in non-small-cell lung cancer (NSCLC) cell lines. MATERIALS AND METHODS: Cell growth inhibition was studied using the Propidium iodide (PI) assay. Cell cycle analysis and recovery were detected by flow cytometry. The expression levels of various proteins were detected by western blot. Inhibition of colony formation in H460 was checked in vitro. In vivo efficacy was studied in H460 xenograft model. RESULTS: The combination of P276-00 and VPA showed synergistic effect on p53+ and p53- NSCLC cell lines in antiproliferative assay at both constant and non-constant ratio with marked decrease in colony forming potential. Flow cytometric analysis confirmed a significant time dependent increase in apoptosis with 64% apoptotic population at 96h compared to VPA (1%) and P276-00 (28%) alone ($p < 0.0001$). Incubation of the cells after treatment, in fresh medium without drugs, led to the recovery of cells treated with P276-00 alone but not the cells treated with the combination of both the drugs. The combination treatment up-regulated tumor suppressor proteins like p53, p21 and p27 along with down-regulation of proliferation and survival proteins viz. cyclin D1 and Bcl-2. This was also associated with the upregulation of the pro-apoptotic protein Bax and significant accumulation of hyperacetylated histones in the combination treatment. Interestingly, VPA in combination with P276-00 was much more effective as an antitumor agent than alone, in the H460 xenograft tumor model in SCID mice. CONCLUSIONS: This study indicates that the combination of HDAC inhibitor VPA with CDK inhibitor P276-00 is promising novel molecularly targeted therapeutic approach for NSCLC treatment.

[530]

TÍTULO / TITLE: - Cetuximab enhances TRAIL-induced gastric cancer cell apoptosis by promoting DISC formation in lipid rafts.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Sep 20;439(2):285-90. doi: 10.1016/j.bbrc.2013.08.040. Epub 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.08.040](https://doi.org/10.1016/j.bbrc.2013.08.040)

AUTORES / AUTHORS: - Xu L; Hu X; Qu X; Hou K; Zheng H; Liu Y

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The First Hospital of China Medical University, Shenyang 110001, China.

RESUMEN / SUMMARY: - TRAIL is a member of the tumor necrosis factor family that selectively induces cancer cell apoptosis. However, gastric cancer cells are insensitive to TRAIL. Our and others studies showed that the inhibition of EGFR pathway activation could increase the sensitivity of TRAIL in cancer cells. But the detailed mechanism is not fully understood. In the present study, compared with TRAIL or cetuximab (an anti-EGFR monoclonal antibody) alone, treatment with the TRAIL/cetuximab combination significantly promoted death receptor 4 (DR4) clustering as well as the translocation of both DR4 and Fas-associated death domain-containing protein (FADD) into lipid rafts. This in turn resulted in caspase-8 cleavage and the formation of the death-inducing signaling complex (DISC) in these lipid rafts. Cholesterol-depletion with methyl-beta-cyclodextrin partially prevented DR4 clustering and DISC formation, and thus partially reversed apoptosis induced by the TRAIL/cetuximab dual treatment. These results indicate that cetuximab increases TRAIL-induced gastric cancer cell apoptosis at least partially through the promotion of DISC formation in lipid rafts.

[531]

TÍTULO / TITLE: - Acid-degradable core-shell nanoparticles for reversed tamoxifen-resistance in breast cancer by silencing manganese superoxide dismutase (MnSOD).

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

REVISTA / JOURNAL: - Biomaterials. 2013 Sep 19. pii: S0142-9612(13)01074-0. doi: 10.1016/j.biomaterials.2013.09.003.

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

[1016/j.biomaterials.2013.09.003](#)

AUTORES / AUTHORS: - Cho SK; Pedram A; Levin ER; Kwon YJ

INSTITUCIÓN / INSTITUTION: - Department of Chemical Engineering and Materials Science, University of California, Irvine, CA 92697, United States.

RESUMEN / SUMMARY: - Drug resistance acquired by cancer cells is a significant challenge in the clinic and requires impairing the responsible pathological pathway. Administering chemotherapeutics along with silencing resistance-basis activity using RNA interference (RNAi) is expected to restore the activity of the chemotherapeutic and generate synergistic cancer eradication. This study attempted to reverse tamoxifen (TAM)-resistance in breast cancer by silencing a mitochondrial enzyme, manganese superoxide dismutase (MnSOD), which dismutates TAM-induced reactive oxygen species (ROS) (i.e., superoxide) to less harmful hydrogen peroxide and hampers therapeutic effects. Breast cancer cells were co-treated with TAM and MnSOD siRNA-delivering nanoparticles (NPs) made of a siRNA/poly(amidoamine) (PAMAM) dendriplex core and an acid-degradable polyketal (PK) shell. The (siRNA/PAMAM)-PK NPs were designed for the PK shell to shield siRNA from nucleases, minimize detrimental aggregation in serum, and facilitate cytosolic release of siRNA from

endosomal compartments. This method of forming the PK shell around the siRNA/PAMAM core via surface-initiated photo-polymerization enables ease of tuning NPs' size for readily controlled siRNA release kinetics. The resulting NPs were notably homogenous in size, resistant to aggregation in serum, and invulnerable to heparan sulfate-mediated disassembly, compared to siRNA/PAMAM dendriplexes. Gel electrophoresis and confocal microscopy confirmed efficient siRNA release from the (siRNA/PAMAM)-PK NPs upon stimuli-responsive hydrolysis of the PK shell. Sensitization of TAM-resistant MCF7-BK-TR breast cancer cells with (MnSOD siRNA/PAMAM)-PK NPs restored TAM-induced cellular apoptosis in vitro and significantly suppressed tumor growth in vivo, as confirmed by biochemical assays and histological observations. This study implies that combined gene silencing and chemotherapy is a promising strategy to overcoming a significant challenge in cancer therapy.

[532]

TÍTULO / TITLE: - MLN2238, a proteasome inhibitor, induces caspase-dependent cell death, cell cycle arrest, and potentiates the cytotoxic activity of chemotherapy agents in rituximab-chemotherapy-sensitive or rituximab-chemotherapy-resistant B-cell lymphoma preclinical models.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Nov;24(10):1030-8. doi: 10.1097/CAD.0000000000000008.

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

[1097/CAD.0000000000000008](#)

AUTORES / AUTHORS: - Gu JJ; Hernandez-Ilizaliturri FJ; Mavis C; Czuczman NM; Deeb G; Gibbs J; Skitzki JJ; Patil R

INSTITUCIÓN / INSTITUTION: - Departments of aMedicine bImmunology cPathology dSurgical Oncology, Roswell Park Cancer Institute, Buffalo, New York, USA.

RESUMEN / SUMMARY: - To further develop therapeutic strategies targeting the proteasome system, we studied the antitumor activity and mechanisms of action of MLN2238, a reversible proteasome inhibitor, in preclinical lymphoma models. Experiments were conducted in rituximab-chemotherapy-sensitive cell lines, rituximab-chemotherapy-resistant cell lines (RRCL), and primary B-cell lymphoma cells. Cells were exposed to MLN2238 or caspase-dependent inhibitors, and differences in cell viability, alterations in apoptotic protein levels, effects on cell cycle, and the possibility of synergy when combined with chemotherapeutic agents were evaluated. MLN2238 showed more potent dose-dependent and time-dependent cytotoxicity and inhibition of cell proliferation in lymphoma cells than bortezomib. Our data suggest that MLN2238 can induce caspase-independent cell death in RRCL. MLN2238 (and to a much lesser degree bortezomib) reduced RRCL S phase and

induced cell cycle arrest in the G2/M phase. Exposure of rituximab-chemotherapy-sensitive cell lines and RRCL to MLN2238 potentiated the cytotoxic effects of gemcitabine, doxorubicin, and paclitaxel and overcame resistance to chemotherapy in RRCL. MLN2238 is a potent proteasome inhibitor active in rituximab-chemotherapy-sensitive and rituximab-chemotherapy-resistant cell models and potentiates the antitumor activity of chemotherapy agents and has the potential of becoming an effective therapeutic agent in the treatment of therapy-resistant B-cell lymphoma.

[533]

TÍTULO / TITLE: - Prognostic Value of Nuclear Translocation of Aryl Hydrocarbon Receptor for Non-small Cell Lung Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3953-61.

AUTORES / AUTHORS: - Su JM; Lin P; Chang H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, School of Medicine, China Medical University, No. 91 Hsueh-Shih Road, Taichung, Taiwan 40402, R.O.C.
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RESUMEN / SUMMARY: - BACKGROUND: The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor which translocates from the cytoplasm to the nucleus after activation. AhR overexpression is positively associated with epidermal growth factor (EGFR) expression in non-small cell lung cancer (NSCLC). The association between AhR expression and types of EGFR mutation, and the prognostic value of AhR expression in NSCLC remain unclear. PATIENTS AND METHODS: The AhR expression and detection of L858R and E746-750^a deletion of EGFR in NSCLC was assessed using immunohistochemistry. RESULTS: Nuclear translocation of AhR was more common in females, non-smokers, adenocarcinoma (AD) and NSCLC patients with EGFR E746-750^a deletion. The overall median survival time (MST) was 20.4 months for patients with NSCLC, 21.8 months for these with AD and 15.4 months for these with squamous cell carcinoma (SQ). The MST was significantly reduced in patients with poor performance status, SQ or advanced cancer stage. AhR nuclear translocation was associated with cancer death in SQ (hazard ratio=3.714, p<0.001) but not in AD (hazard ratio=0.837, p=0.407). CONCLUSION: Nuclear translocation of AhR was associated with EGFR mutation, and conferred a poor prognosis for patients with lung SQ.

[534]

TÍTULO / TITLE: - Interferon beta failure predicted by EMA criteria or isolated MRI activity in multiple sclerosis.

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

REVISTA / JOURNAL: - Mult Scler. 2013 Sep 3.

●● Enlace al texto completo (gratuito o de pago) [1177/1352458513502399](https://doi.org/10.1177/1352458513502399)

AUTORES / AUTHORS: - Prosperini L; Mancinelli CR; De Giglio L; De Angelis F; Barletta V; Pozzilli C

INSTITUCIÓN / INSTITUTION: - Department of Neurology and Psychiatry, Sapienza University, Rome, Italy.

RESUMEN / SUMMARY: - OBJECTIVE: The objective of this paper is to investigate four-year outcomes of interferon beta (IFNB)-treated patients with multiple sclerosis (MS) according to their clinical or magnetic resonance imaging (MRI) activity status at first year of treatment. METHODS: A total of 370 patients with MS duration ≤ 5 years before IFNB start were followed-up for four years. The optimal threshold for one-year MRI activity that more accurately predicted subsequent relapses or disability worsening was identified. The risk of relapses and disability worsening after the first year was then estimated by propensity score (PS)-adjusted analyses in patients fulfilling European Medicines Agency (EMA) criteria for second-line escalation and in those with isolated MRI activity. RESULTS: A total of 192 (51.9%) patients relapsed, and 66 (17.8%) worsened in disability from year 1 to 4 of follow-up. The more accurate threshold for one-year MRI activity was the occurrence of ≥ 1 enhancing or ≥ 2 new T2-lesions. An increased risk of relapses and disability worsening was found in either patients fulfilling EMA criteria (hazard ratio (HR) = 3.69, and HR = 6.02) and in those experiencing isolated MRI activity (HR = 3.15, and HR = 5.31) at first year of treatment, when compared with stable patients (all p values < 0.001). CONCLUSION: The four-year outcomes of patients with isolated MRI activity did not differ from those fulfilling EMA criteria at first year of IFNB treatment.

[535]

TÍTULO / TITLE: - The BRAF V600E mutation in papillary thyroid cancer with positive or suspected pre-surgical cytological finding is not associated with advanced stages or worse prognosis.

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

REVISTA / JOURNAL: - Endocrine. 2013 Aug 8.

●● Enlace al texto completo (gratuito o de pago) [1007/s12020-013-0029-5](https://doi.org/10.1007/s12020-013-0029-5)

AUTORES / AUTHORS: - Barbaro D; Incensati RM; Materazzi G; Boni G; Grosso M; Panicucci E; Lapi P; Pasquini C; Miccoli P

INSTITUCIÓN / INSTITUTION: - Section of Endocrinology, ASL 6 Livorno, Viale Aferi 36, Leghorn, Italy, danielebarbaro1970@libero.it.

RESUMEN / SUMMARY: - The mutation BRAF V600E is thought to be a putative prognostic marker of the aggressiveness of several cancers among which is also papillary thyroid cancer. Our study aimed to evaluate whether this mutation is associated with advanced stages of disease or with a worse prognosis in a series of patients with cytological findings of Thy 4 and Thy 5 and who were undergoing total thyroidectomy

and routine central compartment lymph-node dissection. 110 patients were consecutively enrolled over an 18-month period from September 2010 to March 2012. All patients had cytological findings that were either indicative of, or positive for papillary thyroid cancer, Thy 4 or Thy 5. Detection of BRAF mutation was made on fine-needle aspiration specimen by pyrosequencing after microdissection and DNA extraction of neoplastic cells. After surgical intervention, the patients underwent radioiodine ablation according to our protocol, and follow-up was performed after 8 months. The BRAF V600E mutation was found in 79 % of our cases: 85.7 % of these cases represented the classical variant, 57.8 % the follicular variant, 89.6 % the tall cell variant, and 33.3 % the solid variant. All patients had confirmation of papillary thyroid cancer after histology, with no differences being seen in pTNM presentation between patients with BRAF wild-type and patients with BRAF V600E mutation. Ninety-nine patients underwent radioiodine ablation. Results at follow-up 8 months after radioiodine ablation showed no differences in the rate of ablation between patients harboring BRAF V600E mutation and those having BRAF wild-type. The BRAF V600E mutation doesn't appear to be a reliable risk factor for the aggressiveness of a tumor. BRAF analysis should neither be the only guide for pre-surgical decisions regarding the extent of surgery nor for post-surgical decisions regarding the aggressiveness of the treatment.

[536]

TÍTULO / TITLE: - Apigenin impairs oral squamous cell carcinoma growth in vitro inducing cell cycle arrest and apoptosis.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1675-82. doi: 10.3892/ijo.2013.2072. Epub 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2072](#)

AUTORES / AUTHORS: - Maggioni D; Garavello W; Rigolio R; Pignataro L; Gaini R; Nicolini G

INSTITUCIÓN / INSTITUTION: - Department of Surgery and Translational Medicine, University of Milan-Bicocca, I-20900 Monza, Italy.

RESUMEN / SUMMARY: - In the present study, we investigated the effect of apigenin, a flavonoid widely present in fruits and vegetables, on a tongue oral cancer-derived cell line (SCC-25) and on a keratinocyte cell line (HaCaT), with the aim of unveiling its antiproliferative mechanisms. The effect of apigenin on cell growth was evaluated by MTT assay, while apoptosis was investigated by phosphatidyl serine membrane translocation and cell cycle distribution by propidium iodide DNA staining through flow cytometry. In addition the expression of cyclins and cyclin-dependent kinases was evaluated by western blotting. A reduction of apigenin-induced cell growth was found in both cell lines, although SCC-25 cells were significantly more sensitive than the

immortalized keratinocytes, HaCaT. Moreover, apigenin induced apoptosis and modulated the cell cycle in SCC-25 cells. Apigenin treatment resulted in cell cycle arrest at both G0/G1 and G2/M checkpoints, while western blot analysis revealed the decreased expression of cyclin D1 and E, and inactivation of CDK1 upon apigenin treatment. These results demonstrate the anticancer potential of apigenin in an oral squamous cell carcinoma cell line, suggesting that it may be a very promising chemopreventive agent due to its cancer cell cytotoxic activity and its ability to act as a cell cycle modulating agent at multiple levels.

[537]

TÍTULO / TITLE: - Levels of target activation predict antifibrotic responses to tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Ann Rheum Dis. 2013 Sep 7. doi: 10.1136/annrheumdis-2013-203729.

- Enlace al texto completo (gratis o de pago) [1136/annrheumdis-2013-203729](#)

AUTORES / AUTHORS: - Maurer B; Distler A; Dees C; Khan K; Denton CP; Abraham D; Gay RE; Michel BA; Gay S; Distler JH; Distler O

INSTITUCIÓN / INSTITUTION: - Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

RESUMEN / SUMMARY: - **OBJECTIVES:** To assess whether the discrepancy between the strong antifibrotic effects of tyrosine kinase inhibitors (TKIs) in animal models and the inconsistent results in clinical studies might be related to the activation levels of drug targets. **METHODS:** Skin sections of bleomycin, TSK1, Fra-2 transgenic mice, SSc patients and controls were analysed by histology and immunohistochemistry. Subgroups of mice were treated with the TKIs nilotinib or imatinib. Differences in the activation levels of the TKI targets p-PDGFRbeta (platelet derived growth factor beta) and p-c-abl were assessed. **RESULTS:** In bleomycin and TSK1 mice, expression of activated p-PDGFRbeta (platelet derived growth factor receptor beta) and p-c-abl was ubiquitous with strong upregulation compared with controls. Treatment with TKIs resulted in successful target inhibition and consequently reduced dermal fibrosis. In the Fra-2 model, the activation levels of p-PDGFRbeta and p-c-abl were much lower than in the bleomycin and the TSK1 models. Accordingly, nilotinib did not prevent dermal fibrosis and target inhibition was unsuccessful. Notably, in skin biopsies of SSc patients, the mean activation levels of TKI targets were only moderate and in the majority of patients resembled those of the non-responsive Fra-2 model. **CONCLUSIONS:** Animal models for proof-of-concept studies should be selected based on a similar activation level and expression pattern of drug targets as in human SSc.

[538]

TÍTULO / TITLE: - Histopathology of lung adenocarcinoma based on new IASLC/ATS/ERS classification: Prognostic stratification with functional and metabolic imaging biomarkers.

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

REVISTA / JOURNAL: - J Magn Reson Imaging. 2013 Mar 21. doi: 10.1002/jmri.24080.

●● Enlace al texto completo (gratis o de pago) [1002/jmri.24080](#)

AUTORES / AUTHORS: - Lee HY; Jeong JY; Lee KS; Yi CA; Kim BT; Kang H; Kwon OJ; Shim YM; Han J

INSTITUCIÓN / INSTITUTION: - Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - **PURPOSE:** To correlate the results of histopathologic subtyping and grading of lung adenocarcinoma with maximum standardized uptake values (SUVmax) on positron emission tomography (PET)/computed tomography and apparent diffusion coefficient (ADC) values on diffusion-weighted MRI (DWI). **MATERIALS AND METHODS:** Forty-three patients were included. The SUVmax and mean ADC values of tumors were measured and correlated with the histologic subtypes and grades of lung adenocarcinomas based on the IASLC/ATS/ERS classification scheme. Disease-free survival (DFS) was estimated by using the Kaplan-Meier method, and the log-rank test was used to evaluate differences among three histologic grades or subgroups classified with imaging biomarker study results. **RESULTS:** Five (12.5%) tumors belonged to low grade, 30 (70%) to intermediate grade, and 8 (18.5%) to high grade, and patients with low-grade histology had lower risk of recurrence than those with intermediate- or high-grade histology ($P = 0.048$). A significant difference in SUVmax and mean ADC values was observed among three histologic grades ($P_s < 0.001$). Regarding DFS, lower metabolic (PET) activity or higher functional (DWI) diffusivity showed longer DFS. When patients ($n = 30$; 70% of patients) with intermediate histologic grade were subgrouped in consideration of both SUVmax and mean ADC results, combining metabolic and functional criteria helped stratify patients more precisely ($P = 0.006$). **CONCLUSION:** SUVmax and mean ADC value correlate well with the histologic grades in lung adenocarcinomas, and combining both imaging biomarker study results leads to more useful stratification of patients into different prognostic subsets than the results of each study. J. Magn. Reson. Imaging 2013. Esta es una cita bibliográfica que va por delante de la publicación en papel. La fecha indicada en la cita provista, NO corresponde con la fecha o la cita bibliográfica de la publicación en papel. La cita bibliográfica definitiva (con el volumen y su paginación) saldrá en 1 ó 2 meses a partir de la fecha de la emisión electrónica-online. *** This is a bibliographic record ahead of the paper publication. The given date in the bibliographic record does not correspond to the date or the bibliographic citation on the paper publication. The publisher will provide the final bibliographic

citation (with the volume, and pagination) within 1 or 2 months from the date the record was published online. © 2013 Wiley Periodicals, Inc.

[539]

TÍTULO / TITLE: - Interaction of brain fatty acid-binding protein with the polyunsaturated fatty acid environment as a potential determinant of poor prognosis in malignant glioma.

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

REVISTA / JOURNAL: - Prog Lipid Res. 2013 Aug 24;52(4):562-570. doi: 10.1016/j.plipres.2013.08.004.

●● Enlace al texto completo (gratis o de pago) 1016/j.plipres.2013.08.004

AUTORES / AUTHORS: - Elsherbiny ME; Emara M; Godbout R

INSTITUCIÓN / INSTITUTION: - Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta T6G 1Z2, Canada.

RESUMEN / SUMMARY: - Malignant gliomas are the most common adult brain cancers. In spite of aggressive treatment, recurrence occurs in the great majority of patients and is invariably fatal. Polyunsaturated fatty acids are abundant in brain, particularly omega-6 arachidonic acid (AA) and omega-3 docosahexaenoic acid (DHA). Although the levels of omega-6 and omega-3 polyunsaturated fatty acids are tightly regulated in brain, the omega-6:omega-3 ratio is dramatically increased in malignant glioma, suggesting deregulation of fundamental lipid homeostasis in brain tumor tissue. The migratory properties of malignant glioma cells can be modified by altering the ratio of AA:DHA in growth medium, with increased migration observed in AA-rich medium. This fatty acid-dependent effect on cell migration is dependent on expression of the brain fatty acid binding protein (FABP7) previously shown to bind DHA and AA. Increased levels of enzymes involved in eicosanoid production in FABP7-positive malignant glioma cells suggest that FABP7 is an important modulator of AA metabolism. We provide evidence that increased production of eicosanoids in FABP7-positive malignant glioma growing in an AA-rich environment contributes to tumor infiltration in the brain. We discuss pathways and molecules that may underlie FABP7/AA-mediated promotion of cell migration and FABP7/DHA-mediated inhibition of cell migration in malignant glioma.

[540]

TÍTULO / TITLE: - Tumor Suppressor Secreted Frizzled Related Protein 1 Regulates P53-Mediated Apoptosis.

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

REVISTA / JOURNAL: - Cell Biol Int. 2013 Sep 13. doi: 10.1002/cbin.10176.

●● Enlace al texto completo (gratis o de pago) 1002/cbin.10176

AUTORES / AUTHORS: - Gauger KJ; Schneider SS

INSTITUCIÓN / INSTITUTION: - Pioneer Valley Life Sciences Institute, Baystate Medical Center, Springfield, MA, 01199, USA; Biology Department, University of Massachusetts, Amherst, MA, 01003, USA.

RESUMEN / SUMMARY: - The most frequently occurring cancer in women, and the second leading cause of cancer death among women, is breast cancer. Cancer results from cellular mutations that enhance proliferation and decrease programmed cell death (apoptosis). Secreted Frizzled-Related Proteins (SFRPs) are a family of proteins known for their ability to negatively modulate the Wnt signaling cascade. SFRP1 expression is lost in a multitude of cancers, including breast cancer, and SFRP1 downregulation reduces apoptosis in vitro but the mechanisms remain unclear, as also the effect of Sfrp1 deficiency on apoptosis on mammary epithelial cells in vivo. Our data show that mammary glands from Sfrp1^{-/-} mice express significantly less Bcl2l11 (Bim) and Bax mRNA in response to DNA damage. The effect of Sfrp1 loss in reducing gamma-irradiation induced apoptosis was examined by TUNEL staining and cleaved-caspase-3 immunostaining. The findings show that Sfrp1^{-/-} mice have less DNA fragmentation, whilst caspase-3 expression is activated, and that p53 expression is generally diminished. Recombinant SFRP1 could replace endogenous expression and elevate the levels of pro-apoptotic and p53-mediated gene expression (Bcl2l, Bax, Cdkn1a, and Bbc3) in mammary epithelial cells derived from Sfrp1^{-/-} mice. Thus Sfrp1 plays an important role in mediating mammary epithelial apoptotic response to DNA damage in vivo. The role SFRP1 plays in p53 target gene expression was also noted, which suggests that this pathway may be worth exploiting for novel therapies.

[541]

TÍTULO / TITLE: - A mechanically coupled reaction-diffusion model for predicting the response of breast tumors to neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Phys Med Biol. 2013 Sep 7;58(17):5851-66. doi: 10.1088/0031-9155/58/17/5851. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1088/0031-9155/58/17/5851](#)

AUTORES / AUTHORS: - Weis JA; Miga MI; Arlinghaus LR; Li X; Chakravarthy AB; Abramson V; Farley J; Yankeelov TE

INSTITUCIÓN / INSTITUTION: - Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA. Departments of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, USA.

RESUMEN / SUMMARY: - There is currently a paucity of reliable techniques for predicting the response of breast tumors to neoadjuvant chemotherapy. The standard approach is to monitor gross changes in tumor size as measured by physical exam and/or conventional imaging, but these methods generally do not show whether a tumor is responding until the patient has received many treatment cycles. One promising

approach to address this clinical need is to integrate quantitative in vivo imaging data into biomathematical models of tumor growth in order to predict eventual response based on early measurements during therapy. In this work, we illustrate a novel biomechanical mathematical modeling approach in which contrast enhanced and diffusion weighted magnetic resonance imaging data acquired before and after the first cycle of neoadjuvant therapy are used to calibrate a patient-specific response model which subsequently is used to predict patient outcome at the conclusion of therapy. We present a modification of the reaction-diffusion tumor growth model whereby mechanical coupling to the surrounding tissue stiffness is incorporated via restricted cell diffusion. We use simulations and experimental data to illustrate how incorporating tissue mechanical properties leads to qualitatively and quantitatively different tumor growth patterns than when such properties are ignored. We apply the approach to patient data in a preliminary dataset of eight patients exhibiting a varying degree of responsiveness to neoadjuvant therapy, and we show that the mechanically coupled reaction-diffusion tumor growth model, when projected forward, more accurately predicts residual tumor burden at the conclusion of therapy than the non-mechanically coupled model. The mechanically coupled model predictions exhibit a significant correlation with data observations (PCC = 0.84, $p < 0.01$), and show a statistically significant >4 fold reduction in model/data error ($p = 0.02$) as compared to the non-mechanically coupled model.

[542]

TÍTULO / TITLE: - A binuclear complex constituted by diethyldithiocarbamate and copper(I) functions as a proteasome activity inhibitor in pancreatic cancer cultures and xenografts.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Sep 20. pii: S0041-008X(13)00409-2. doi: 10.1016/j.taap.2013.09.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.09.009](#)

AUTORES / AUTHORS: - Han J; Liu L; Yue X; Chang J; Hua Y

INSTITUCIÓN / INSTITUTION: - Department of Integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China; Shanghai Clinical Center, Chinese Academy of Sciences/Xuhui Central Hospital, Shanghai 200031, China.

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RESUMEN / SUMMARY: - It is a therapeutic strategy for cancers including pancreatic to inhibit proteasome activity. Disulfiram (DSF) may bind copper (Cu) to form a DSF-Cu complex. DSF-Cu is capable of inducing apoptosis in cancer cells by inhibiting proteasome activity. DSF is rapidly converted to diethyldithiocarbamate (DDTC) within bodies. Copper(II) absorbed by bodies is reduced to copper(I) when it enters cells. We

found that DDTC and copper(I) could form a binuclear complex which might be entitled DDTC-Cu(I), and it had been synthesized by us in the laboratory. This study is to investigate the anticancer potential of this complex on pancreatic cancer and the possible mechanism. Pancreatic cancer cell lines, SW1990, PANC-1 and BXP-3 were used for in vitro assays. Female athymic nude mice grown SW1990 xenografts were used as animal models. Cell counting kit-8 (cck-8) assay and flow cytometry were used for analyzing apoptosis in cells. A 20S proteasome assay kit was used in proteasome activity analysis. Western blot (WB) and immunohistochemistry (IHC) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assays were used in tumor sample analysis. The results suggest that DDTC-Cu(I) inhibit pancreatic cancer cell proliferation and proteasome activity in vitro and in vivo. Accumulation of ubiquitinated proteins, and increased p27 as well as decreased NF-kappaB expression were detected in tumor tissues of DDTC-Cu(I)-treated group. Our data indicates that DDTC-Cu(I) is an effective proteasome activity inhibitor with the potential to be explored as a drug for pancreatic cancer.

[543]

TÍTULO / TITLE: - Identification of human leucocyte antigen (HLA)-A*0201-restricted cytotoxic T lymphocyte epitopes derived from HLA-DOBeta as a novel target for multiple myeloma.

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

REVISTA / JOURNAL: - Br J Haematol. 2013 Aug 30. doi: 10.1111/bjh.12544.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12544](#)

AUTORES / AUTHORS: - Kang YJ; Zeng W; Song W; Reinhold B; Choi J; Brusic V; Yamashita T; Munshi A; Li C; Minvielle S; Anderson KC; Munshi N; Reinherz EL; Sasada T

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; Cancer Vaccine Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; Department of Biomedical Science, Jungwon University, Chungcheongbuk-do, South Korea.

RESUMEN / SUMMARY: - Despite the recent development of effective therapeutic agents against multiple myeloma (MM), new therapeutic approaches, including immunotherapies, remain to be developed. Here we identified novel human leucocyte antigen (HLA)-A*0201 (HLA-A2)-restricted cytotoxic T lymphocyte (CTL) epitopes from a B cell specific molecule HLA-DOBeta (DOB) as a potential target for MM. By DNA microarray analysis, the HLA-DOB expression in MM cells was significantly higher than that in normal plasma cells. Twenty-five peptides were predicted to bind to HLA-A2 from the amino acid sequence of HLA-DOB. When screened for the immunogenicity in HLA-A2-transgenic mice immunized with HLA-DOB cDNA, 4 peptides were substantially immunogenic. By mass spectrometry analysis of peptides eluted from HLA-A2-immunoprecipitates of MM cell lines, only two epitopes, HLA-DOB232-240 (FLLGLIFLL)

and HLA-DOB185-193 (VMLEMTPEL), were confirmed for their physical presence on cell surface. When healthy donor blood was repeatedly stimulated in vitro with these two peptides and assessed by antigen-specific gamma-interferon secretion, HLA-DOB232-240 was more immunogenic than HLA-DOB185-193 . Additionally, the HLA-DOB232-240 -specific CTLs, but not the HLA-DOB185-193 -specific CTLs, displayed an major histocompatibility complex class I-restricted reactivity against MM cell lines expressing both HLA-A2 and HLA-DOB. Taken together, based on the physical presence on tumour cell surface and high immunogenicity, HLA-DOB232-240 might be useful for developing a novel immunotherapy against MM.

[544]

TÍTULO / TITLE: - Non-genomic events determining the sensitivity of hemopoietic malignancies to glucocorticoid-induced apoptosis.

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

REVISTA / JOURNAL: - Cancer Immunol Immunother. 2013 Sep 26.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00262-013-1477-8](#)

AUTORES / AUTHORS: - Kfir-Erenfeld S; Yefenof E

INSTITUCIÓN / INSTITUTION: - The Lautenberg Center for Immunology and Cancer Research, IMRIC, The Hebrew University-Hadassah Medical School, POB: 12272, 91120, Jerusalem, Israel, shlomit.kfir@mail.huji.ac.il.

RESUMEN / SUMMARY: - Glucocorticoid (GC) hormones have been introduced as therapeutic agents in blood cancers six decades ago. The effectiveness of GC treatment stems from its ability to induce apoptotic death of hemopoietic cells. A major impediment in GC therapy is the acquisition of resistance to the drug upon repeated treatment. In addition, some blood cancers are a priori resistant to GC therapy. Usually, resistance to GC correlates with poor prognosis. Albeit the wide use of GC in clinical practice, their mode of action is not fully understood. The cellular response to GC is initiated by its binding to the cytosolic GC receptor (GR) that translocates to the nucleus and modulates gene expression. However, nuclear activities of GR occur in both apoptosis-sensitive and apoptosis-resistant cells. These apparent controversies can be resolved by deciphering non-genomic effects of GCs and the mode by which they modulate the apoptotic response. We suggest that non-genomic consequences of GC stimulation determine the cell fate toward survival or death. Understanding the cellular mechanisms of GC apoptotic sensitivity contributes to the development of new modalities for overcoming GC resistance.

[545]

TÍTULO / TITLE: - Site-specific PEGylation of a mutated-cysteine residue and its effect on tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL).

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

REVISTA / JOURNAL: - Biomaterials. 2013 Dec;34(36):9115-23. doi: 10.1016/j.biomaterials.2013.08.020. Epub 2013 Aug 24.

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

[1016/j.biomaterials.2013.08.020](#)

AUTORES / AUTHORS: - Pan LQ; Wang HB; Lai J; Xu YC; Zhang C; Chen SQ

INSTITUCIÓN / INSTITUTION: - Institute of Pharmacology, Toxicology and Biochemical Pharmaceutics, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China.

RESUMEN / SUMMARY: - Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a promising antitumor agent that specifically induces apoptosis in broad-spectrum tumor cell lines, meanwhile leaving normal cells unaffected. Unfortunately, the clinical development of TRAIL was hampered, and could be attributed to its instability, bioavailability or poor delivery. Although N-terminal specific PEGylation provides a means to improve the pharmacokinetic and stability of TRAIL, it took a bit longer time to accomplish the PEGylation process than expected. We therefore designed another PEGylation approach, mutated Cys-SH site-specific PEGylation, to conjugate methoxypoly(ethylene glycol) maleimide (mPEG-MAL) with TRAIL (95-281) mutant N109C. Asn-109 was chosen as the PEGylated site for it is a potential N-linked glycosylation site. It was shown that approximately 90% TRAIL mutant N109C could be PEGylated by mPEG-MAL within 40 min. And mPEGMAL-N109C was revealed to possess superior in vitro stability and antitumor activity than N-terminal specifically PEGylated TRAIL (114-281) (mPEGALD-TRAIL114-281). What's more, mPEGMAL-N109C exhibited more therapeutic potentials than mPEGALD-TRAIL114-281 in tumor xenograft model, benefitting from better drug delivery and bioavailability. These results have demonstrated mutated Cys-SH specific PEGylation is an alternative to site-specifically PEGylate TRAIL efficiently and effectively other than N-terminal specific PEGylation.

[546]

TÍTULO / TITLE: - Interferon-gamma in ascites could be a predictive biomarker of outcome in ovarian carcinoma.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Aug 1. pii: S0090-8258(13)01070-6. doi: 10.1016/j.ygyno.2013.07.105.

●● Enlace al texto completo (gratis o de pago) [1016/j.ygyno.2013.07.105](#)

AUTORES / AUTHORS: - Chen YL; Cheng WF; Chang MC; Lin HW; Huang CT; Chien CL; Chen CA

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Anatomy and Cell Biology, College of Medicine, National Taiwan University, Taipei, Taiwan; Gynecologic Cancer Center,

Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan;
Department of Obstetrics and Gynecology, College of Medicine, National Taiwan University, Taipei, Taiwan.

RESUMEN / SUMMARY: - OBJECTIVE: The ovarian cancer-associated ascites is an ideal material for evaluating the interaction between the host immune system and cancer cells in the tumor micro-environment. The aim of this study was to investigate whether the selected target cytokine expression levels in ascites could serve as an immune biomarker for predicting outcomes in ovarian cancer. METHODS: Eighty-eight specimens of ovarian cancer-associated ascites were evaluated to select the target cytokine by a cytokine profiling kit. The 144 total samples were subsequently analyzed for this target cytokine. The correlation between the target cytokine and clinical characteristics was analyzed. RESULTS: Interferon-gamma (IFN-gamma) was identified as the target cytokine. Higher levels of IFN-gamma in the ascites of the tumor micro-environment were associated with advanced disease ($p=0.012$), higher tumor histological grading ($p=0.004$), and sub-optimal surgical status ($p=0.040$). By multivariate analysis, the adjusted hazard ratios (HRs) were 2.74 (95% confidence interval (CI) 1.85-4.05, $p<0.001$) for disease-free survival (DFS) and 1.72 (95% CI 1.01-2.93, $p=0.048$) for overall survival (OS) for a 10-fold increase in IFN-gamma concentration in the ascites. An inverse dose-response relationship between IFN-gamma level and survival was also noted ($P_{trend}<0.001$ for DFS and $P_{trend}<0.042$ for OS). CONCLUSIONS: Patients with ovarian cancer and higher IFN-gamma expression levels in cancer-associated ascites will have shorter DFS and OS. IFN-gamma levels in the ascites may be a prognostic marker and a potential reference for immunotherapy targeting IFN-gamma.

[547]

TÍTULO / TITLE: - Azacitidine induces profound genome-wide hypomethylation in primary myelodysplastic bone marrow cultures but may also reduce histone acetylation.

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

REVISTA / JOURNAL: - Leukemia. 2013 Sep 12. doi: 10.1038/leu.2013.265.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.265](#)

AUTORES / AUTHORS: - Grovdal M; Karimi M; Tobiasson M; Reinius L; Jansson M; Ekwall K; Ungerstedt J; Kere J; Greco D; Hellstrom-Lindberg E

INSTITUCIÓN / INSTITUTION: - Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden.

[548]

TÍTULO / TITLE: - Dual Phosphatidylinositol-3-Kinase/Mammalian Target of Rapamycin Inhibitor NVP-BEZ235 Sensitizes Docetaxel in Castration Resistant Prostate Cancer.

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

REVISTA / JOURNAL: - J Urol. 2013 Aug 14. pii: S0022-5347(13)05128-8. doi: 10.1016/j.juro.2013.07.101.

●● Enlace al texto completo (gratis o de pago) 1016/j.juro.2013.07.101

AUTORES / AUTHORS: - Yasumizu Y; Miyajima A; Kosaka T; Miyazaki Y; Kikuchi E; Oya M

INSTITUCIÓN / INSTITUTION: - The Department of Urology, Keio University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - PURPOSE: The development of effective therapeutic strategies that can achieve long-term improvement in patients with castration resistant prostate cancer (CRPC) is urgently needed. Recently we demonstrated that the activated PI3K/Akt/mTOR signaling pathway induced by docetaxel explains the resistance to docetaxel in CRPC. The aim of this study was to explore the efficacy of NVP-BEZ235, a dual PI3K and mTORC1/2 inhibitor, for docetaxel resistant CRPC. MATERIALS AND METHODS: We used two human CRPC cell lines: C4-2 and C4-2AT6 cells. C4-2AT6 cells were established from C4-2 in our laboratory under androgen-ablated treatment for 6 months. We investigated the efficacy of NVP-BEZ235 monotherapy and NVP-BEZ235 combined with docetaxel in vitro and in vivo. RESULTS: The elevated phosphorylated Akt in C4-2AT6 cells was significantly inhibited by NVP-BEZ235 in a dose- and time-dependent manner. WST cell proliferation assay results in C4-2AT6 cells revealed combined administration of NVP-BEZ235 and docetaxel had a significant and synergistically higher cytotoxicity than NVP-BEZ235 monotherapy or docetaxel monotherapy. Combined NVP-BEZ235 (40 mg/kg) and docetaxel (4 mg/kg) in vivo using a castrated mice xenograft model inhibited C4-2AT6 tumor growth to a greater degree compared to the monotherapy groups. Also, NVP-BEZ235 showed significant efficacy with docetaxel at a low concentration in vivo, suggesting NVP-BEZ235 was effective at reducing the resistance to docetaxel. CONCLUSIONS: These results suggest that inhibition of the PI3K/Akt/mTOR signaling pathway by NVP-BEZ235 can overcome docetaxel resistance in human CRPC. Our findings provide a molecular basis for the clinical use of combined administration of NVP-BEZ235 and docetaxel in CRPC patients.

[549]

TÍTULO / TITLE: - Targeting SHP2 for EGFR inhibitor resistant non-small cell lung carcinoma.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Oct 4;439(4):586-590. doi: 10.1016/j.bbrc.2013.09.028. Epub 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.09.028

AUTORES / AUTHORS: - Xu J; Zeng LF; Shen W; Turchi JJ; Zhang ZY

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, United States.

RESUMEN / SUMMARY: - Targeted therapy with inhibitors of epidermal growth factor receptor (EGFR) has produced a noticeable benefit to non-small cell lung cancer (NSCLC) patients whose tumors carry activating mutations (e.g. L858R) in EGFR. Unfortunately, these patients develop drug resistance after treatment, due to acquired secondary gatekeeper mutations in EGFR (e.g. T790M). Given the critical role of SHP2 in growth factor receptor signaling, we sought to determine whether targeting SHP2 could have therapeutic value for EGFR inhibitor resistant NSCLC. We show that SHP2 is required for EGF-stimulated ERK1/2 phosphorylation and proliferation in EGFR inhibitor resistant NSCLC cell line H1975, which harbors the EGFR T790M/L858R double-mutant. We demonstrate that treatment of H1975 cells with II-B08, a specific SHP2 inhibitor, phenocopies the observed growth inhibition and reduced ERK1/2 activation seen in cells treated with SHP2 siRNA. Importantly, we also find that II-B08 exhibits marked anti-tumor activity in H1975 xenograft mice. Finally, we observe that combined inhibition of SHP2 and PI3K impairs both the ERK1/2 and PI3K/AKT signaling axes and produces significantly greater effects on repressing H1975 cell growth than inhibition of either protein individually. Collectively, these results suggest that targeting SHP2 may represent an effective strategy for treatment of EGFR inhibitor resistant NSCLCs.

[550]

TÍTULO / TITLE: - The effect of sea anemone (*H. magnifica*) venom on two human breast cancer lines: death by apoptosis.

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

REVISTA / JOURNAL: - Cytotechnology. 2013 Aug 30.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10616-013-9636-5](#)

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.

RESUMEN / SUMMARY: - Venom from the sea anemone, *Heteractis magnifica*, has multiple biological effects including, cytotoxic, cytolytic and hemolytic activities. In this study, cytotoxicity induced by *H. magnifica* venom was investigated using the crystal violet assay on human breast cancer T47D and MCF7 cell lines and normal human breast 184B5 cell line. Apoptosis was also assayed via Annexin V-fluorescein isothiocyanate and propidium iodide (PI) staining followed by flow cytometric analysis. Cell cycle progression and mitochondria membrane potential were studied via flow cytometry following PI and JC-1 staining respectively. *H. magnifica* venom induced significant reductions in viable cell numbers and increases in apoptosis in T47D and

MCF7 in dose-dependent manners. A significant apoptosis-related increase in the sub G1 peak of the cell cycle in both breast cancer cell lines was also observed. Moreover, treatment by venom cleaved caspase-8, caspase-9, and activated caspase-3. Overall, H. magnifica venom was highly cytotoxic to T47D and MCF7 human breast cancer cells, and the phenomenon could be the killing phenomenon via the death receptor-mediated and the mitochondria-mediated apoptotic pathways. Consequently, H. magnifica venom has potential for the development of a breast cancer therapeutic.

[551]

TÍTULO / TITLE: - A tumor necrosis factor-alpha inhibitor reduces the embryotoxic effects of endometriotic peritoneal fluid.

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

REVISTA / JOURNAL: - Fertil Steril. 2013 Sep 4. pii: S0015-0282(13)02771-4. doi: 10.1016/j.fertnstert.2013.07.1985.

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

[1016/j.fertnstert.2013.07.1985](#)

AUTORES / AUTHORS: - Chen YJ; Wu HH; Liau WT; Tsai CY; Tsai HW; Chao KC; Sung YJ; Li HY

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan; Division of Obstetrics and Gynecology, Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

RESUMEN / SUMMARY: - **OBJECTIVE:** To determine whether a tumor necrosis factor-alpha (TNF-alpha) inhibitor can reduce the embryotoxicity of the peritoneal fluid (PF) of women with endometriosis. **DESIGN:** Experimental clinical study. **SETTING:** University hospital. **PATIENT(S):** Twelve women with chocolate cysts and 12 control women without endometriosis. **INTERVENTION(S):** None. **MAIN OUTCOME MEASURE(S):** We collected the PF from patients with chocolate cysts (CH-PF) and patients without endometriosis (N-PF) during laparoscopic surgery. For the in vitro studies, development and apoptosis were evaluated in two-cell stage mouse embryos after incubation with CH-PF and N-PF, with or without a TNF-alpha inhibitor. **RESULT(S):** We found that CH-PF significantly decreased the rate of blastocyst development and increased the percentage of apoptotic cells in the embryos. Cytokine assays showed that the concentrations of several cytokines, including TNF-alpha, were higher in embryos incubated with CH-PF than in those incubated with N-PF. Furthermore, the treatment of embryos with TNF-alpha retarded development and induced apoptosis. Importantly, adalimumab, a TNF-alpha inhibitor, effectively abrogated the embryotoxicity that was induced by CH-PF. **CONCLUSION(S):** These data collectively highlight the crucial role of TNF-alpha in CH-PF-induced embryotoxicity and suggest that TNF-alpha inhibitors may be potential therapeutic agents for treating endometriosis-induced infertility.

[552]

TÍTULO / TITLE: - Anticancer and immunostimulatory role of encapsulated tumor antigen containing cobalt oxide nanoparticles.

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

REVISTA / JOURNAL: - J Biol Inorg Chem. 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1007/s00775-013-1044-y](#)

AUTORES / AUTHORS: - Chattopadhyay S; Dash SK; Ghosh T; Das S; Tripathy S; Mandal D; Das D; Pramanik P; Roy S

INSTITUCIÓN / INSTITUTION: - Immunology and Microbiology Laboratory, Department of Human Physiology with Community Health, Vidyasagar University, Midnapore, 721102, West Bengal, India.

RESUMEN / SUMMARY: - The purpose of this study is to evaluate the prospect of using surface modified cobalt oxide (CoO) nanoparticles as carriers of cancer antigens to human macrophages. N-Phosnomethyliminodiacetic acid (PMIDA) was used for surface modification to overcome the toxic effect of CoO nanoparticles. Here, the phosphonate group of the PMIDA acts as a surface-anchoring agent and the remaining -COOH groups bind nonspecifically with tumor associated antigens. This modification allows the conjugation of human oral carcinoma (KB) cell lysate (CL) as an antigen with PMIDA coated CoO nanoparticles (CL-PMIDA-CoO). Particle characterization was performed by dynamic light scattering, atomic force microscopy, and scanning electron microscopy studies. Fourier transform IR spectroscopy was used to investigate conjugation of the protein with nanoparticles. Protein encapsulation was confirmed by protein gel electrophoresis. Active uptake of antigen-conjugated nanoparticles by macrophages was confirmed by fluorescence microscopy. The antitumor activity of the nanocomplex pulsed macrophages was investigated on a human oral carcinoma cell line (KB) in vitro. The modified nanocomplexes upregulate IFN-gamma and TNF-alpha and induce an anticancer immune response by activating macrophages. The use of TNF-alpha inhibitor confirmed the ability of the CL-PMIDA-CoO nanocomplex to stimulate TNF-alpha mediated immunostimulation. CL-PMIDA-CoO nanoparticles efficiently increased the CD4+ population. Thus, our findings provide insight into the use of PMIDA coated CoO nanoparticles as antigen delivery vehicles.

[553]

TÍTULO / TITLE: - Ursolic acid inhibits colorectal cancer angiogenesis through suppression of multiple signaling pathways.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1666-74. doi: 10.3892/ijo.2013.2101. Epub 2013 Sep 16.

- Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2101](https://doi.org/10.3892/ijo.2013.2101)

AUTORES / AUTHORS: - Lin J; Chen Y; Wei L; Hong Z; Sferra TJ

INSTITUCIÓN / INSTITUTION: - Academy of Integrative Medicine Biomedical Research Center, Fujian University of Traditional Chinese Medicine, Minhou Shangjie, Fuzhou, Fujian 350122, P.R. China.

RESUMEN / SUMMARY: - Angiogenesis plays a critical role in the development of solid tumors by supplying nutrients and oxygen to support continuous growth of tumor as well as providing an avenue for hematogenous metastasis. Tumor angiogenesis is highly regulated by multiple intracellular signaling transduction cascades such as Hedgehog, STAT3, Akt and p70S6K pathways that are known to malfunction in many types of cancer including colorectal cancer (CRC). Therefore, suppression of tumor angiogenesis through targeting these signaling pathways has become a promising strategy for cancer chemotherapy. Ursolic acid (UA) is a major active compound present in many medicinal herbs that have long been used in China for the clinical treatment of various types of cancer. Although previous studies have demonstrated an antitumor effect for UA, the precise mechanisms of its anti-angiogenic activity are not well understood. To further elucidate the mechanism(s) of the tumoricidal activity of UA, using a CRC mouse xenograft model, chick embryo chorioallantoic membrane (CAM) model, the human colon carcinoma cell line HT-29 and human umbilical vein endothelial cells (HUVECs), in the present study we evaluated the efficacy of UA against tumor growth and angiogenesis in vivo and in vitro and investigated the underlying molecular mechanisms. We found that administration of UA significantly inhibited tumor volume but had no effect on body weight changes in CRC mice, suggesting that UA can suppress colon cancer growth in vivo without noticeable signs of toxicity. In addition, UA treatment reduced intratumoral microvessel density (MVD) in CRC mice, decreased the total number of blood vessels in the CAM model, and dose and time-dependently inhibited the proliferation, migration and tube formation of HUVECs, demonstrating UA's antitumor angiogenesis in vivo and in vitro. Moreover, UA treatment inhibited the expression of critical angiogenic factors, such as VEGF-A and bFGF. Furthermore, UA suppressed the activation of sonic hedgehog (SHH), STAT3, Akt and p70S6K pathways. Collectively, our findings suggest that inhibition of tumor angiogenesis via suppression of multiple signaling pathways might be one of the mechanisms whereby UA can be effective in cancer treatment.

[554]

TÍTULO / TITLE: - Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 5.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-1142-z](https://doi.org/10.1007/s13277-013-1142-z)

AUTORES / AUTHORS: - Sun M; Xia R; Jin F; Xu T; Liu Z; De W; Liu X

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Nanjing Medical University, Nanjing, 210029, Jiangsu, People's Republic of China.

RESUMEN / SUMMARY: - Long noncoding RNAs (lncRNAs) have emerged recently as major players in governing fundamental biological processes, and many of which are altered in expression and likely to have a functional role in tumorigenesis. Maternally expressed gene 3 (MEG3) is an imprinted gene located at 14q32 that encodes a lncRNA associated with various human cancers. However, its biological role and clinical significance in gastric cancer development and progression are unknown. In this study, to investigate the lncRNA MEG3 expression in gastric cancer, quantitative reverse-transcription polymerase chain reaction was conducted. We found that MEG3 levels were markedly decreased in gastric cancer tissues compared with adjacent normal tissues. Its expression level was significantly correlated with TNM stages, depth of invasion, and tumor size. Moreover, patients with low levels of MEG3 expression had a relatively poor prognosis. Furthermore, knockdown of MEG3 expression by siRNA could promote cell proliferation, while ectopic expression of MEG3 inhibited cell proliferation, promoted cell apoptosis, and modulated p53 expression in gastric cancer cell lines. By 5-aza-CdR treatment, we also observed that MEG3 expression can be modulated by DNA methylation. Our findings present that MEG3 downexpression can be identified as a poor prognostic biomarker in gastric cancer and regulate cell proliferation and apoptosis in vitro.

[555]

TÍTULO / TITLE: - Inhibitory effects of a major soy isoflavone, genistein, on human DNA topoisomerase II activity and cancer cell proliferation.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Oct;43(4):1117-24. doi: 10.3892/ijo.2013.2032. Epub 2013 Jul 23.

●● [Enlace al texto completo \(gratuito o de pago\) 3892/ijo.2013.2032](#)

AUTORES / AUTHORS: - Mizushima Y; Shiomi K; Kuriyama I; Takahashi Y; Yoshida H

INSTITUCIÓN / INSTITUTION: - Laboratory of Food and Nutritional Sciences, Faculty of Nutrition, Kobe Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan.

RESUMEN / SUMMARY: - The inhibitory activity of 3 soy isoflavones (daidzein, genistein and glycitein) and their glycosides (daidzin, genistin and glycitin) on mammalian DNA polymerases (pols) and topoisomerases (topos) was investigated. Of the compounds tested, only genistein selectively inhibited human topo II activity and had an IC50 value of 37.5 microM. These isoflavones had no effect on the activity of human topo I; mammalian pols alpha, beta, gamma and kappa; or on any other DNA metabolic enzyme tested. Thermal transition analysis indicated that genistein did not influence the direct binding to double-stranded DNA. Genistein prevented the proliferation of

HCT116 human colon carcinoma cells with an LD50 of 94.0 microM and it halted the cell cycle in G2/M phase. These results suggest that decreases in cell proliferation due to genistein may result from the inhibition of cellular topo II and that genistein, a major soy isoflavone, may be an anticancer food component. The relationship between the structures and these bioactivities of soy isoflavones is discussed.

[556]

TÍTULO / TITLE: - Time to prostate specific antigen (PSA) nadir may predict rapid relapse in men with metastatic castration-resistant prostate cancer (CRPC) receiving docetaxel chemotherapy.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Dec;30(4):719. doi: 10.1007/s12032-013-0719-0. Epub 2013 Sep 12.

●● [Enlace al texto completo \(gratuito o de pago\) 1007/s12032-013-0719-0](#)

AUTORES / AUTHORS: - Thomas BM; Smith C; Evans J; Button MR; Kumar S; Palaniappan N; Staffurth J; Tanguay JS; Lester JF

INSTITUCIÓN / INSTITUTION: - Velindre Cancer Centre, Velindre NHS Trust, Velindre Road, Whitchurch, Cardiff, CF14 2TL, UK, betsanthomas@doctors.net.uk.

RESUMEN / SUMMARY: - Docetaxel has been shown to improve survival in patients with metastatic castrate-resistant prostate cancer (mCRPC). There is no clear consensus regarding the optimum duration of chemotherapy. If patients at greater risk of rapid disease relapse could be identified when on chemotherapy, appropriate follow-up strategies could be put into place. The aim of our study was to find prostate specific antigen (PSA) characteristics that predict a shorter disease response to docetaxel chemotherapy. Data from 41 consecutive mCRPC patients treated with three-weekly docetaxel chemotherapy at a single centre between February 2010 and February 2012 were retrospectively analysed. All patients had $\geq 50\%$ reduction in their PSA with chemotherapy. The relationship between time to PSA nadir (TTN) and PSA halving time with time to PSA progression and overall chemotherapy response duration was analysed. TTN was a strong predictor of the duration of chemotherapy response and time to PSA progression. When TTN was ≥ 16 weeks, the mean duration of response to chemotherapy was 37.5 weeks compared to 19.9 weeks when TTN < 16 weeks (95 % CI, 12.66-22.60; $p = 1.239 \times 10^{-8}$). The mean time to PSA progression was 12.8 weeks if TTN was ≥ 16 weeks and 8.2 weeks TTN was < 16 weeks (95 % CI 0.63-8.60; $p = 0.024$). We observed that a TTN from the initiation of chemotherapy of < 16 weeks for patients with mCRPC is an independent predictor of shorter duration of response and shorter progression-free survival.

[557]

TÍTULO / TITLE: - HDLs protect the MIN6 insulinoma cell line against tunicamycin-induced apoptosis without inhibiting ER stress and without restoring ER functionality.

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

REVISTA / JOURNAL: - Mol Cell Endocrinol. 2013 Aug 28;381(1-2):291-301. doi: 10.1016/j.mce.2013.08.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.mce.2013.08.016](#)

AUTORES / AUTHORS: - Puyal J; Petremand J; Dubuis G; Rummel C; Widmann C

INSTITUCIÓN / INSTITUTION: - Department of Fundamental Neurosciences, University of Lausanne, Switzerland.

RESUMEN / SUMMARY: - HDLs protect pancreatic beta cells against apoptosis induced by several endoplasmic reticulum (ER) stressors, including thapsigargin, cyclopiazonic acid, palmitate and insulin over-expression. This protection is mediated by the capacity of HDLs to maintain proper ER morphology and ER functions such as protein folding and trafficking. Here, we identified a distinct mode of protection exerted by HDLs in beta cells challenged with tunicamycin™, a protein glycosylation inhibitor inducing ER stress. HDLs were found to inhibit apoptosis induced by TM in the MIN6 insulinoma cell line and this correlated with the maintenance of a normal ER morphology. Surprisingly however, this protective response was neither associated with a significant ER stress reduction, nor with restoration of protein folding and trafficking in the ER. These data indicate that HDLs can use at least two mechanisms to protect beta cells against ER stressors. One that relies on the maintenance of ER function and one that operates independently of ER function modulation. The capacity of HDLs to activate several anti-apoptotic pathways in beta cells may explain their ability to efficiently protect these cells against a variety of insults.

[558]

TÍTULO / TITLE: - A standardized extract from Paeonia lactiflora and Astragalus membranaceus induces apoptosis and inhibits the proliferation, migration and invasion of human hepatoma cell lines.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Nov;43(5):1643-51. doi: 10.3892/ijo.2013.2085. Epub 2013 Aug 30.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2085](#)

AUTORES / AUTHORS: - Wu JJ; Sun WY; Hu SS; Zhang S; Wei W

INSTITUCIÓN / INSTITUTION: - Institute of Clinical Pharmacology, Anhui Medical University, Key Laboratory of Antiinflammatory and Immune Medicine, Ministry of Education, Engineering Technology Research Center of Anti-inflammatory and Immunodrugs in Anhui Province, Hefei, Anhui 230032, P.R. China.

RESUMEN / SUMMARY: - Paeonia lactiflora and Astragalus membranaceus are two traditional Chinese medicines, which are commonly used in Chinese herb prescription

to treat liver diseases. The protective effects of the extract prepared from the roots of *Paeonia lactiflora* and *Astragalus membranaceus* (PAE) on liver fibrosis have been demonstrated in previous studies. However, its effect on hepatocellular carcinoma (HCC) has not been investigated to date. In this study, the effects of PAE on the apoptosis, proliferation, migration and invasion of the human hepatoma cell lines HepG2 and SMMC-7721 were investigated. Our data demonstrated that treatment with PAE (50-200 mg/l) caused an inhibitory effect on the proliferation of the hepatoma cell lines HepG2 and SMMC-7721. Furthermore, PAE induced apoptosis of HepG2 cells and SMMC-7721 cells, which was demonstrated by PI staining. In addition, immunocytochemistry and western blotting showed that PAE significantly decreased the expression of Bcl-2, while the expression of Bax and cleaved caspase-3 in HepG2 cells and SMMC-7721 cells was significantly increased after treatment with PAE. These results clearly demonstrated that PAE induced hepatoma cell apoptosis through increasing the Bax-to-Bcl-2 ratio and upregulating the activation of caspase-3. In addition, the results of wound healing assay and Matrigel invasion assay showed that PAE displayed inhibitory activity on the migration and invasion of HCC cells. Taken together, the present data provides evidence that PAE is a potent antineoplastic drug candidate for the treatment of HCC.

[559]

TÍTULO / TITLE: - High level of preoperative carbohydrate antigen 19-9 is a poor survival predictor in gastric cancer.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Aug 28;19(32):5302-8. doi: 10.3748/wjg.v19.i32.5302.

●● [Enlace al texto completo \(gratis o de pago\) 3748/wjg.v19.i32.5302](#)

AUTORES / AUTHORS: - Choi AR; Park JC; Kim JH; Lee SK; Lee YC; Chung JB

INSTITUCIÓN / INSTITUTION: - A Ra Choi, Jun Chul Park, Jie-Hyun Kim, Sung Kwan Shin, Sang Kil Lee, Yong Chan Lee, Jae Bock Chung, Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, Seoul 120-752, South Korea.

RESUMEN / SUMMARY: - AIM: To assess the clinical significance and the prognostic value of preoperative serum carbohydrate antigen 19-9 (CA 19-9) level in gastric cancer. METHODS: Between January 2005 and December 2006, 1960 patients underwent surgery for histologically confirmed gastric cancer. Of these, 163 patients had elevated serum levels of CA 19-9 preoperatively, and 1628 patients had normal serum levels of CA 19-9 preoperatively. For this study, 325 patients were selected from the group of 1628 patients by age, sex, and cancer stage to serve as controls. Statistically significant differences in survival rates were calculated using the log-rank test. A P value less than 0.05 was considered statistically significant and was determined using SAS software.

RESULTS: The baseline characteristics showed some differences between the two groups with regard to histology. Overall survival (OS) in the elevated and non-elevated group was 37.90 and 68.67 mo, respectively ($P < 0.001$). N stage ($P = 0.001$) was a significant predictor of disease-free survival by multivariate analysis. Also, N stage ($P < 0.001$), and the presence of peritoneal metastasis ($P < 0.001$) remained independent factors in predicting OS by multivariate analysis. Additionally, preoperative serum CA 19-9 levels were significantly associated with OS in univariate ($P = 0.009$) and multivariate ($P = 0.021$) analyses. CONCLUSION: Serum CA 19-9 can be considered an independent prognostic factor in predicting OS in patients anticipating surgery for gastric cancer.

[560]

TÍTULO / TITLE: - Bruton tyrosine kinase is commonly overexpressed in mantle cell lymphoma and its attenuation by Ibrutinib induces apoptosis.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Oct;37(10):1271-7. doi: 10.1016/j.leukres.2013.07.028. Epub 2013 Aug 17.

●● Enlace al texto completo (gratis o de pago) [1016/j.leukres.2013.07.028](#)

AUTORES / AUTHORS: - Cinar M; Hamedani F; Mo Z; Cinar B; Amin HM; Alkan S

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, United States.

RESUMEN / SUMMARY: - Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy that characteristically shows overexpression of cyclin-D1 due to an alteration in the t(11;14)(q13;q32) chromosomal region. Although there are some promising treatment modalities, great majority of patients with this disease remain incurable. The B-cell antigen receptor (BCR) signaling plays a crucial role in B-cell biology and lymphomagenesis. Bruton tyrosine kinase (BTK) has been identified as a key component of the BCR signaling pathway. Evidence suggests that the blockade of BTK activity by potent pharmacologic inhibitors attenuates BCR signaling and induces cell death. Notably, the expression levels and the role of BTK in MCL survival are still elusive. Here, we demonstrated a moderate to strong BTK expression in all MCL cases (n=19) compared to benign lymphoid tissues. Treatment of MCL cell lines (Mino or Jeko-1) with a potent BTK pharmacologic inhibitor, Ibrutinib, decreased phospho-BTK-Tyr(223) expression. Consistent with this observation, Ibrutinib inhibited the viability of both Mino and JeKo-1 cells in concentration- and time-dependent manners. Ibrutinib also induced a concentration-dependent apoptosis in both cell lines. Consistently, Ibrutinib treatment decreased the levels of anti-apoptotic Bcl-2, Bcl-xL, and Mcl-1 protein. These findings suggest that BTK signaling plays a critical role in MCL cell survival, and the targeting of BTK could represent a promising therapeutic modality for aggressive lymphoma.

[561]

TÍTULO / TITLE: - Differential regulation of sunitinib targets predicts its tumor-type-specific effect on endothelial and/or tumor cell apoptosis.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2300-0](#)

AUTORES / AUTHORS: - Bousquet G; Varna M; Ferreira I; Wang L; Mongiat-Artus P; Leboeuf C; de Bazelaire C; Faivre S; Bertheau P; Raymond E; Germain S; Janin A

INSTITUCIÓN / INSTITUTION: - Sorbonne Paris Cite, Laboratoire de Pathologie, UMR-S728, Université Paris Diderot, 75010, Paris, France.

RESUMEN / SUMMARY: - PURPOSE: Sunitinib is an inhibitor of tyrosine-kinase receptors, and no biomarker predictive of sunitinib response is available. The purpose of this preclinical study was to show whether sunitinib molecular targets could be used as biomarkers to assess tumor response to sunitinib in human cancer cell line xenografts of three different tumor types. METHODS: Using mice xenografted with liver, breast and renal carcinoma cell lines, we sequentially analyzed the effect of 7-day sunitinib treatment on tumor and vascular compartments. RESULTS: In all xenografts, microvessel damage occurred from Day 1. Tumor damage also occurred in liver, breast, but not in renal xenografts. Using specific human and mouse probes for genes encoding sunitinib targets, we showed a significant relation between apoptotic tumor cell numbers and human PDGFRBeta and RET mRNA expression in liver cancer and to human VEGFR2 expression in breast cancer xenografts. In contrast, in renal cancer xenografts, vascular effect evaluated by measuring endothelial cell apoptosis was related to mouse Vegfr1, Vegfr2 and Vegfa-164 expression. CONCLUSION: This study identifies sunitinib vascular and tumor effects according to different tumor types and shows that sunitinib molecular targets used as biomarkers enable assessment of therapeutic response.

[562]

TÍTULO / TITLE: - Alterations in the EGFR pathway coincide in colorectal cancer and impact on prognosis.

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

REVISTA / JOURNAL: - Virchows Arch. 2013 Oct;463(4):509-523. Epub 2013 Aug 10.

●● Enlace al texto completo (gratis o de pago) [1007/s00428-013-1450-0](#)

AUTORES / AUTHORS: - Neumann J; Wehweck L; Maatz S; Engel J; Kirchner T; Jung A

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Ludwig-Maximilians-Universität München, Thalkirchner Strasse 36, 80337, Munich, Germany, jens.neumann@med.uni-muenchen.de.

RESUMEN / SUMMARY: - Alterations of the downstream effectors of the epidermal growth factor receptor (EGFR) are common events in colorectal cancer (CRC) carcinogenesis. Since EGFR serves as a target for therapy and some downstream effectors of EGFR have predictive and prognostic impact, reliable information on the frequency and concordance of alterations in the signaling pathway has become clinically significant. We, therefore, determined the frequency and coincidence of mutations in the EGFR pathway. We also analyzed the concordance of these alterations between primary tumor and distant metastases. Furthermore, we assessed their prognostic relevance for the development of metastasis. Mutations of KRAS exon 2, BRAF exons 11 and 15, AKT exon 3, and PIK3CA exons 9 and 20 were analyzed by pyrosequencing in 171 primary CRC samples as well as in 63 corresponding metastases. Furthermore, the expression of PTEN and EGFR was assessed by immunohistochemistry. Of the 171 tumors investigated, 60.2 % showed mutations in one or more genes of pathways downstream of EGFR. KRAS exon 2 and BRAF exon 15 mutations were detected in 40.9 and 11.1 % of cases, respectively, and were mutually exclusive. Mutations in exons 9 and 20 of the PIK3CA gene (18.7 %) largely overlapped with exon 2 KRAS mutations (16 of 32 cases; 50.0 %) and, to a lesser extent, with exon 15 mutations of BRAF (2 of 32 cases; 6.3 %). Only one case had simultaneous mutations of AKT exon 3 (0.6 %) and BRAF exon 15. Mutation analysis for KRAS exon 2, BRAF exon 15, PIK3CA exon 20, and AKT exon 3 in primary tumors and in their corresponding metastases revealed 100 % concordance. In one case, a PIK3CA exon 9 mutation in the primary tumor could not be detected in the matched distant metastases ($\kappa = 0.9$). Three different scores were applied for the evaluation of EGFR immunohistochemistry, and the range of positive cases varied between 8.8 and 52.6 %. Loss of PTEN expression was detected in 38.6 %. Although the expression of both markers does coincide with KRAS exon 2, BRAF exon 15, AKT exon 3, and PIK3CA exons 9 and 20 mutations, high discordance rates were found. The presence of at least one alteration in downstream effectors of the EGFR pathway was associated with a higher rate of distant metastases ($p = 0.002$). PIK3CA exons 9 and 20 mutations overlap with KRAS exon 2 and BRAF exon 15 mutations, and BRAF exon 15 and AKT exon 3 mutations co-occur in a single tumor, whereas KRAS exon 2 and BRAF exon 15 mutations are mutually exclusive. This suggests that mutations in the PIK3CA/PTEN/AKT branch of the EGFR pathway are less important than those of the RAS/RAF/MAPK branch for the progression of CRC. We found no difference in the mutational status of KRAS exon 2, BRAF exon 15, and AKT exon 3 between primary tumor and distant metastasis, validating both for diagnostic purposes. PIK3CA exons 9 and 20 mutations can be discordant between primary tumor and distant metastasis, and therefore, the lesion which is targeted for therapy should be tested. Protein expression of PTEN and EGFR using current protocols yields highly discordant results, and better standardization is needed before these markers can be used for diagnostic purposes.

[563]

TÍTULO / TITLE: - WWTR1 promotes cell proliferation and inhibits apoptosis through cyclin A and CTGF regulation in non-small cell lung cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1064-9](#)

AUTORES / AUTHORS: - Wang L; Chen Z; Wang Y; Chang D; Su L; Guo Y; Liu C

INSTITUCIÓN / INSTITUTION: - Nanlou Respiratory Diseases Department, Chinese PLA General Hospital, Beijing, 100853, China.

RESUMEN / SUMMARY: - The Hippo pathway plays a major role in development and organ size control, and its dysregulation contributes to tumorigenesis. WWTR1 is a transcription coactivator acting downstream of the Hippo pathway. Recently, WWTR1 has been reported to be overexpressed in several human cancers including lung cancer. However, the molecular mechanism of WWTR1 regulating lung cancer aggressiveness remains ambiguous. In the present study, we analyzed the expression of WWTR1 in NSCLC cell lines and found that WWTR1 was overexpressed at both the mRNA and protein levels. Knockdown of WWTR1 by siRNA interference in A549 cells significantly inhibited cell proliferation and increased paclitaxel-induced apoptosis. On the other side, WWTR1 overexpression in HBE cell line promoted cell proliferation and inhibited apoptosis. In addition, we found that the decreased proliferation after siRNA treatment was due to cell cycle arrest. Further analysis showed that WWTR1 could induce cyclin A, connective tissue growth factor (CTGF) expression, and inhibit caspase3 cleavage. In conclusion, WWTR1 promotes malignant cell growth and inhibits apoptosis by cyclin A and CTGF regulation.

[564]

TÍTULO / TITLE: - Lymphoma and Epstein-Barr virus DNA in blood during interleukin-2 therapy in antiretroviral-naive HIV-1-infected patients: a substudy of the ANRS 119 trial.

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

REVISTA / JOURNAL: - HIV Med. 2013 Sep 6. doi: 10.1111/hiv.12077.

●● Enlace al texto completo (gratis o de pago) [1111/hiv.12077](#)

AUTORES / AUTHORS: - de Lastours V; Legoff J; Briere J; Agbalika F; Boulet T; Levy Y; Simon F; Aboulker JP; Molina JM

INSTITUCIÓN / INSTITUTION: - Department of Infectious Diseases, Saint-Louis Hospital, Paris, France; University Paris Diderot, Sorbonne Paris Cite, Paris, France.

RESUMEN / SUMMARY: - OBJECTIVES: Interleukin-2 (IL-2) therapy increased CD4 cell counts and delayed antiretroviral therapy (ART) initiation in HIV-infected patients in

the Agence Nationale de Recherche sur le SIDA et les Hepatites Virales (ANRS) 119 trial. However, four cases of lymphoma were reported. Epstein-Barr virus (EBV) replication is associated with an increased risk of lymphoma in immunocompromised patients. We assessed whether IL-2 had an impact on EBV replication and the development of lymphoma. METHODS: A total of 130 ART-naive patients were randomized to receive IL-2 therapy (n = 66) or no treatment (n = 64). Clinical data for patients with lymphomas were reviewed and tumours assessed for evidence of EBV infection and CD25 (the IL-2 receptor) expression. EBV DNA levels were measured in whole blood and plasma in both arms using real-time polymerase chain reaction (PCR), up to 48 weeks after baseline (BL). RESULTS: Four lymphomas occurred, a median of 61 weeks [range 40-94 weeks] after randomization at a median CD4 cell count of 396 cells/ μ L (IQR 234-536 cells/ μ L). In the IL-2 arm, two patients developed EBV-positive Hodgkin's lymphoma, and one developed EBV-negative Burkitt-type lymphoma. One patient in the control group developed EBV-positive non-Hodgkin's lymphoma. CD25 was negative in all cases. Among the 41 of 55 (control arm) and 44 of 58 (IL-2 arm) patients with detectable EBV DNA in whole blood at both BL and week 48, the median change in EBV DNA between BL and week 48 was +0.04 log₁₀ copies/ml in both arms (P = 0.7). In plasma, EBV was detected at least once in 22 of 52 controls and 21 of 54 IL-2-treated patients (P = 0.8). CONCLUSIONS: IL-2 therapy had no significant effect on EBV replication over 48 weeks in these ART-naive patients. The occurrence of lymphomas did not seem to be associated with IL-2 therapy.

[565]

TÍTULO / TITLE: - Role of tumor necrosis factor-alpha, interferon-gamma and Fas-ligand on in vitro nitric oxide activity in the corpus luteum.

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

REVISTA / JOURNAL: - Cytokine. 2013 Oct;64(1):18-21. doi: 10.1016/j.cyto.2013.07.015. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) 1016/j.cyto.2013.07.015

AUTORES / AUTHORS: - Galvao AM; Szostek AZ; Skarzynski DJ; Ferreira-Dias GM

INSTITUCIÓN / INSTITUTION: - CIISA, Faculty of Veterinary Medicine, Technical University of Lisbon, Lisbon, Portugal; Department of Reproductive Immunology and Pathology, Institute of Animal Reproduction and Food Research, Olsztyn, Poland. Electronic address: agalvao@fmv.utl.pt.

RESUMEN / SUMMARY: - Normal reproductive function involves the expression of inflammatory mediators. Regarding the corpus luteum (CL), cytokines promote the cross-talk between immune, vascular and steroidogenic cells, among others. Moreover, TNF, IFNG and FASL were shown to regulate equine CL establishment and regression. We hypothesized that cytokines action on equine CL may be mediated by nitric oxide (NO), through the regulation of endothelial NO synthase (eNOS)

expression. TNF increased eNOS mRNA level and NO metabolite (nitrite) production during CL growth. Cytokines combined action (TNF+IFNG+FASL) promoted eNOS protein upregulation in mid-CL and nitrite production in mid and late-CL. However, in late-CL, TNF alone decreased nitrite secretion. These results indicate that in equine CL, cytokines TNF, IFNG and FASL regulate NO activity, via eNOS expression modulation.

[566]

TÍTULO / TITLE: - Providing activation-induced cytidine deaminase (AID) to nuclear export inhibitors. Response to: "Complex downstream effects of nuclear export inhibition in B-cell lymphomas: a possible role for activation-induced cytidine deaminase".

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

REVISTA / JOURNAL: - Haematologica. 2013 Sep;98(9):e123. doi: 10.3324/haematol.2013.095299.

●● Enlace al texto completo (gratis o de pago) [3324/haematol.2013.095299](#)

AUTORES / AUTHORS: - Azmi AS; Mohammad RM

INSTITUCIÓN / INSTITUTION: - azmia@karmanos.org; mohammar@karmanos.org.

[567]

TÍTULO / TITLE: - Osteopontin is associated with decreased apoptosis and alphav integrin expression in lung adenocarcinoma.

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

REVISTA / JOURNAL: - Acta Histochem. 2013 Aug 29. pii: S0065-1281(13)00148-7. doi: 10.1016/j.acthis.2013.07.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.acthis.2013.07.009](#)

AUTORES / AUTHORS: - Stemberger C; Matusan-Ilijas K; Avirovic M; Bulat-Kardum L; Ivancic A; Jonjic N; Lucin K

INSTITUCIÓN / INSTITUTION: - Department of Clinical Cytology, Clinical Hospital Center Rijeka, Rijeka, Croatia.

RESUMEN / SUMMARY: - Osteopontin (OPN) is a glycoprotein involved in invasion, progression and metastasis of many carcinomas. It contains several functional domains including binding sites for alphav integrins, cell surface molecules playing a major role in mediating cell migration and adhesion. The aim of the study was to evaluate the expression of osteopontin in human non-small cell lung cancer (NSCLC) and to determine its possible prognostic significance as well as relation to apoptosis and alphav integrin expression. We analyzed 111 surgically resected NSCLC for immunohistochemical expression of OPN and alphav integrin. OPN expression was compared to apoptotic rate and clinicopathological parameters such as tumor size, histological grade, lymph node status, pT, and TNM stage. Apoptotic rate was

measured by TUNEL staining method. OPN expression in NSCLC was significantly higher in lung adenocarcinomas (AC) than in squamous cell carcinomas ($p < 0.001$). There was no correlation between OPN expression and clinicopathological parameters. The level of OPN expression in AC was associated with decreased apoptotic activity of tumor cells ($p = 0.006$), and correlated with αv integrin expression ($p = 0.048$), particularly in low stage tumors ($p = 0.013$). Prolonged tumor cell survival in lung AC due to OPN and αv integrin overexpression may have an impact on tumor progression and resistance to therapy.

[568]

TÍTULO / TITLE: - The prognostic significance of Jun transcription factors in ovarian cancer.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Oct;139(10):1673-80. doi: 10.1007/s00432-013-1489-y. Epub 2013 Aug 13.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s00432-013-1489-y](#)

AUTORES / AUTHORS: - Eckhoff K; Flurschutz R; Trillsch F; Mahner S; Janicke F; Milde-Langosch K

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Bldg. N27, 20246, Hamburg, Germany.

RESUMEN / SUMMARY: - **PURPOSE:** The Jun proteins (c-Jun, JunD and JunB) play an important role in the regulation of cell proliferation, apoptosis and angiogenesis. It is well established that these proteins participate in the carcinogenesis and progression in several tumour types. However, little is known about the prognostic significance of Jun proteins in patients with invasive epithelial ovarian carcinoma. **METHODS:** We analysed fresh-frozen tissues of 161 ovarian cancer patients by using Western blot analysis to investigate protein levels of JunB, JunD, c-Jun and phosphorylated c-Jun (pc-Jun Ser63). The results were correlated with clinicopathologic prognostic parameters and survival data. **RESULTS:** A high pc-Jun expression was significantly associated with shorter progression-free survival (14 vs. 16 months, $p = 0.017$) and overall survival (25 vs. 41 months, $p = 0.038$). In case of JunD, moderate protein levels were associated with a better prognosis, leading to longer progression-free and overall survival compared to weak or strong JunD expression (PFS in cases with weak/moderate/strong JunD expression: 14 vs. 19.5 vs. 16 months, $p = 0.011$; OAS: 32 vs. 42 vs. 35.5 months, $p = 0.009$). Multivariate Cox regression analysis confirmed an independent and significant impact of pc-Jun and JunD on the patient's prognosis. **CONCLUSIONS:** Our results show that Jun proteins (pc-Jun and JunD) influence carcinogenesis and tumour progression, suggesting a significant role as prognostic predictors in human ovarian carcinoma.

[569]

TÍTULO / TITLE: - Tanespimycin and Tipifarnib Exhibit Synergism in Inducing Apoptosis in Melanoma Cell Lines From Later Stages of Tumor Progression.

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

REVISTA / JOURNAL: - Cancer Invest. 2013 Oct;31(8):545-549. Epub 2013 Sep 25.

●● Enlace al texto completo (gratis o de pago) [3109/07357907.2013.830736](#)

AUTORES / AUTHORS: - Bentke A; Malecki J; Ostrowska B; Krzykowska-Petitjean K; Laidler P

INSTITUCIÓN / INSTITUTION: - Chair of Medical Biochemistry, Jagiellonian University Medical College, ul. Kopernika 7, Krakow, Poland.

RESUMEN / SUMMARY: - Many anticancer strategies rely on efficient induction of apoptosis. The need for development of drug combinations with a strong pro-apoptotic activity is of particular interest in melanoma resistant to currently available chemotherapeutic regimens. We studied the pro-apoptotic properties of combination of tanespimycin + tipifarnib in five melanoma cell lines representing various stages of tumor progression. Our results show that in cells derived from vertical- and metastatic-phase the combination of tested drugs is strongly cytotoxic and efficient in inducing apoptosis, as evidenced by activation of caspase-9 and caspase-3 and enhanced fragmentation of DNA.

[570]

TÍTULO / TITLE: - Responsiveness of cytogenetically discrete human myeloma cell lines to lenalidomide: lack of correlation with cereblon and interferon regulatory factor 4 expression levels.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Sep 2. doi: 10.1111/ejh.12192.

●● Enlace al texto completo (gratis o de pago) [1111/ejh.12192](#)

AUTORES / AUTHORS: - Greenberg AJ; Walters DK; Kumar SK; Vincent Rajkumar S; Jelinek DF

INSTITUCIÓN / INSTITUTION: - Center for Translational Science Activities, Mayo Clinic, Rochester, MN, USA; Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

RESUMEN / SUMMARY: - The introduction of novel immunomodulatory drugs (IMiDs) has dramatically improved the survival of patients with multiple myeloma (MM). While it has been shown that patients with specific cytogenetic subtypes, namely t(4;14), have the best outcomes when treated with bortezomib-based regimens, the relationship between cytogenetic subtypes and response to IMiDs remains unclear. Using DNA synthesis assays, we investigated the relationship between cytogenetic subtype and lenalidomide response in a representative panel of human myeloma cell lines (HMCLs).

We examined HMCL protein expression levels of the lenalidomide target cereblon (CRBN) and its downstream target interferon regulatory factor-4 (IRF4), which have previously been shown to be predictive of lenalidomide response in HMCLs. Our results reveal that lenalidomide response did not correlate with specific cytogenetic translocations. There were distinct groups of lenalidomide-responsive and non-responsive HMCLs, as defined by inhibition of cellular proliferation; notably, all of the hyperdiploid HMCLs fell into the latter category. Repeated dosing of lenalidomide significantly lowered the IC50 of the responsive HMCL ALMC-1 (IC50 = 2.6 μm vs. 0.005 μm , $P < 0.0001$), but did not have an effect on the IC50 of the non-responsive DP-6 HMCL ($P > 0.05$). Moreover, no association was found between lenalidomide responsiveness and CRBN and IRF4 expression. Our data indicate that lenalidomide sensitivity is independent of cytogenetic subtype in HMCLs. While CRBN and IRF4 have been shown to be associated with response to lenalidomide in patients, these findings do not translate back to HMCLs, which could be attributable to factors present in the bone marrow microenvironment.

[571]

TÍTULO / TITLE: - Utility of ATP7B in Prediction of Response to Platinum-based Chemotherapy in Urothelial Bladder Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3731-7.

AUTORES / AUTHORS: - Schmid SC; Schuster T; Horn T; Gschwend J; Treiber U; Weirich G

INSTITUCIÓN / INSTITUTION: - Urologische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany.

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RESUMEN / SUMMARY: - BACKGROUND: Platinum-based chemotherapy is the treatment of choice for metastatic urothelial carcinoma, which is limited by primary and secondary resistance of the tumour. The Cu(2+) transporting beta polypeptide ATPase (ATP7B) is believed to play a role in this resistance. The aim of this study was to screen the ATP7B gene for mutations and loss of heterozygosity in bladder cancer and to evaluate their impact on chemotherapy resistance. MATERIALS AND METHODS: DNA extracted from 17 patients with metastatic bladder cancer was analyzed by DNA sequencing, and microsatellite analysis. RESULTS: We found 12 non-synonymous mutations and 20 synonymous mutations out of which 11 and 15, respectively, have not been previously described. Results were correlated with response to platinum-based chemotherapy: 65% of patients exhibited LOH of the ATP7B locus on chromosome 13q14.3, with a tendency to have a better response to chemotherapy. CONCLUSION: Although resistance is complex, LOH at the ATP7B locus might be useful in predicting chemotherapy response and needs further evaluation.

[572]

TÍTULO / TITLE: - Multifunctional nanoparticles co-delivering Trp2 peptide and CpG adjuvant induce potent cytotoxic T-lymphocyte response against melanoma and its lung metastasis.

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

REVISTA / JOURNAL: - J Control Release. 2013 Sep 1;172(1):259-265. doi: 10.1016/j.jconrel.2013.08.021.

●● Enlace al texto completo (gratis o de pago) [1016/j.jconrel.2013.08.021](https://doi.org/10.1016/j.jconrel.2013.08.021)

AUTORES / AUTHORS: - Xu Z; Ramishetti S; Tseng YC; Guo S; Huang L

INSTITUCIÓN / INSTITUTION: - Division of Molecular Pharmaceutics, Center for Nanotechnology in Drug Delivery, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.

RESUMEN / SUMMARY: - Immunotherapy has shown the potential to become an essential component of the successful treatment of various malignancies. In many cases, such as in melanoma, however, induction of a potent and specific T-cell response against the endogenous antigen or self-antigen still remains a major challenge. To induce a potent MHC I-restricted cytotoxic T-lymphocyte (CTL) response, cytosol delivery of an exogenous antigen into dendritic cells is preferred, if not required. Lipid-calcium-phosphate (LCP) nanoparticles represent a new class of intracellular delivery systems for impermeable drugs. We are interested in exploring the potential of LCP NPs for use as a peptide vaccine delivery system for cancer therapy. To increase the encapsulation of Trp2 peptide into the calcium phosphate precipitate core of LCP, two phosphor-serine residues were added to the N-terminal of the peptide (p-Trp2). CpG ODN was also co-encapsulated with p-Trp2 as an adjuvant. The NPs were further modified with mannose to enhance and prolong the cargo deposit into the lymph nodes (LNs), which ensured persistent antigen loading and stimulation. Compared with free Trp2 peptide/CpG, vaccination with LCP encapsulating p-Trp2 and CpG resulted in superior inhibition of tumor growth in both B16F10 subcutaneous and lung metastasis models. An IFN-gamma production assay and in vivo CTL response study revealed that the improved efficacy was a result of a Trp2-specific immune response. Thus, encapsulation of phospho-peptide antigens into LCP may be a promising strategy for enhancing the immunogenicity of poorly immunogenic self-antigens for cancer therapy.

[573]

TÍTULO / TITLE: - Pulsed high-intensity focused ultrasound enhances apoptosis of pancreatic cancer xenograft with gemcitabine.

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

REVISTA / JOURNAL: - Ultrasound Med Biol. 2013 Nov;39(11):1991-2000. doi: 10.1016/j.ultrasmedbio.2013.06.004. Epub 2013 Aug 22.

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

[1016/j.ultrasmedbio.2013.06.004](https://doi.org/10.1016/j.ultrasmedbio.2013.06.004)

AUTORES / AUTHORS: - Lee ES; Lee JY; Kim H; Choi Y; Park J; Han JK; Choi BI

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Seoul National University Hospital, Seoul, Korea.

RESUMEN / SUMMARY: - We sought to investigate whether concurrent exposure to pulsed high-intensity focused ultrasound (HIFU) and the chemotherapeutic drug gemcitabine would enhance apoptosis in pancreatic cancer. A pancreatic cancer xenograft model was established using BALB/c nude mice and human pancreatic cancer cells (PANC-1). In the first study, mice were randomly allocated into one of four groups: control (n = 4), HIFU alone (n = 4), gemcitabine (GEM) alone (n = 28) and concurrent treatment with HIFU and gemcitabine (HIGEM) (n = 28). The GEM and HIGEM groups were subdivided into four subgroups (16 mice) according to the drug dose injected (50-200 mg/kg) and another four subgroups (16 mice) according to the time interval between drug injection and HIFU treatment (each subgroup, n = 4). Apoptosis rates were evaluated using the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling) assay and percentage of necrosis, as evaluated with Harris' hematoxylin solution and eosin Y stain, 3 d after treatment. The second study was performed to evaluate tumor growth rates of the four groups. Each group was treated weekly for 3 wk, and tumor size was periodically measured for up to 4 wk from the beginning of treatment. In the first study, overall rates of apoptosis were significantly higher in the HIGEM group than in the GEM group (p = 0.02). In a subgroup analysis, HIGEM was superior to GEM in enhancing apoptosis at gemcitabine dosages of 150-200 mg/kg gemcitabine and intervals between gemcitabine and HIFU less than 2 h (p = 0.01). In the second study, HIGEM treatment resulted in the slowest tumor growth. However, despite a visible distinction, none of the differences found between the HIGEM and GEM groups were statistically significant (p > 0.05). Treatment with both HIFU and gemcitabine might enhance cell apoptosis and reduce tumor growth in pancreatic carcinoma. For this concurrent treatment, a high dosage of gemcitabine and a short-term delay before HIFU are recommended to maximize the therapeutic effect.

[574]

TÍTULO / TITLE: - Anti-proliferative and apoptosis inducing effect of nimbolide by altering molecules involved in apoptosis and IGF signalling via PI3K/Akt in prostate cancer (PC-3) cell line.

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

REVISTA / JOURNAL: - Cell Biochem Funct. 2013 Aug 21. doi: 10.1002/cbf.2993.

- Enlace al texto completo (gratis o de pago) [1002/cbf.2993](https://doi.org/10.1002/cbf.2993)

AUTORES / AUTHORS: - Raja Singh P; Arunkumar R; Sivakamasundari V; Sharmila G; Elumalai P; Suganthapriya E; Brindha Mercy A; Senthilkumar K; Arunakaran J

INSTITUCIÓN / INSTITUTION: - Department of Endocrinology, Dr ALM Post Graduate Institute of Basic Medical Sciences, University of Madras, Chennai, Tamilnadu, India.

RESUMEN / SUMMARY: - Prostate cancer is responsible for major deaths globally after lung cancer. Nimbolide is an important constituent of neem, and it acts as a potent inhibitor for many cancer cells. The present study was designed to evaluate the effects of nimbolide on apoptosis and insulin-like growth factor (IGF) signalling molecules in androgen-independent prostate cancer (PC-3) cells line. Nimbolide (0.5-2 μ M) treatment resulted in 50% inhibition at a dose of 2 μ M in the PC-3 cell line. The mRNA expression of Fas ligand, Fas-associated death domain receptor (FADD), Bcl-2-associated X protein (Bax), Bcl-2-associated death promoter (Bad), phosphatidylinositide 3-kinases (PI3K), Akt, IGF1, IGF1 receptor (IGF1R) and IGF binding protein 3 were quantified by reverse transcription polymerase chain reaction and protein expression of Bax, cytochrome c, X-linked inhibitor of apoptosis protein (XIAP), B-Cell Lymphoma 2 (Bcl-2), caspases -8, -9, -10 and -3, poly(ADP-ribose) polymerase (PARP), cleaved PARP, IGF1R, PI3K, Akt, p-Akt was determined by western blot analysis, in nimbolide-treated PC-3 cell line. Nimbolide-induced apoptosis by activating DNA fragmentation in PC-3 cells. Nimbolide treatment increased the mRNA of Fas ligand, FADD, Bax, Bad and IGF binding protein 3, decreased PI3K, Akt, IGF1 and IGF1R, increased protein expression of caspases 8, 3, 10, 9, Bax and cytochrome c and decreased the expression of XIAP, Bcl2, cleaved PARP, p-Akt and IGF1R. The results suggest that nimbolide acts as a potent anti-cancer agent by inducing apoptosis and inhibiting cell proliferation via PI3K/Akt pathway in PC-3 cells. Copyright © 2013 John Wiley & Sons, Ltd.

[575]

TÍTULO / TITLE: - Expression of tumor necrosis factor-like weak inducer of apoptosis in human middle ear cholesteatoma.

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

REVISTA / JOURNAL: - ORL J Otorhinolaryngol Relat Spec. 2013;75(4):221-7. doi: 10.1159/000351552. Epub 2013 Jul 26.

- Enlace al texto completo (gratis o de pago) [1159/000351552](https://doi.org/10.1159/000351552)

AUTORES / AUTHORS: - Park M; Lee B; Lee J

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology, Head and Neck Surgery, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea.

RESUMEN / SUMMARY: - Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) was recently identified as a member of the TNF superfamily of structurally related cytokines. It regulates TNF-alpha and numerous cellular responses. We

investigated whether TWEAK is upregulated in human middle ear cholesteatoma compared to the skin of the normal external auditory canal (EAC). The expression of TWEAK was analyzed using reverse transcription-polymerase chain reaction, Western blotting and immunohistochemical staining. TWEAK expression was correlated with that of TNF-alpha as determined by Western blotting. The expression of TWEAK and TNF-alpha protein was stronger in cholesteatoma tissue than in EAC skin. TWEAK was expressed to a greater degree in the suprabasal layer in the cholesteatoma than in EAC skin. The expression of TWEAK was correlated more closely with single-stranded DNA than Ki-67 immunohistochemically. These findings imply that TWEAK plays an important role in modulating TNF-alpha expression and apoptosis in cholesteatoma. © 2013 S. Karger AG, Basel.

[576]

TÍTULO / TITLE: - A potential new enriching trial design for selecting non-small-cell lung cancer patients with no predictive biomarker for trials based on both histology and early tumor response: further analysis of a thalidomide trial.

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

REVISTA / JOURNAL: - Cancer Med. 2013 Jun;2(3):360-6. doi: 10.1002/cam4.74. Epub 2013 Apr 24.

●● Enlace al texto completo (gratis o de pago) [1002/cam4.74](#)

AUTORES / AUTHORS: - Lee SM; Hackshaw A

INSTITUCIÓN / INSTITUTION: - Department of Oncology, University College London (UCL) Hospitals and UCL Cancer Institute, 250 Euston Road, London, NW1 2PG, United Kingdom. sm.lee@uclh.nhs.uk

RESUMEN / SUMMARY: - There are few predictive biomarkers for antiangiogenic trials in lung cancer. We examine a potential treatment strategy in which a patient group is enriched using both histology and an early assessment of response during standard chemotherapy, and where a new agent is given for the remainder of chemotherapy and as maintenance. We performed a retrospective analysis of 722 stage IIIB/IV non-small-cell lung cancer patients from a double-blind placebo-controlled trial of thalidomide or placebo 100-200 mg/day, combined with gemcitabine/carboplatin (for up to four cycles), then given as single agent maintenance therapy. There was a significant statistical interaction between treatment and histology, with a possible benefit among squamous cell cancer (SCC) patients. We examined 150 SCC patients who were “nonprogressors” (stable disease or complete/partial response) after completing the second chemotherapy cycle. Endpoints were progression-free survival (PFS) and overall survival (OS). Among the 150 patients nonprogressors after cycle 2 (thalidomide, n = 72; placebo, n = 78; baseline characteristics were similar), the hazard ratios (HRs) were: OS = 0.76 (95% CI: 0.54-1.07) and PFS = 0.69 (95% CI: 0.50-0.97). In 57 patients who had a complete/partial response, the HRs were: OS = 0.63 (95% CI:

0.34-1.15) and PFS = 0.50 (95% CI: 0.28-0.88). SCC patients who were nonprogressors after 2 cycles of standard chemotherapy showed evidence of a benefit from thalidomide when taken for the remainder of chemotherapy and as maintenance. This strategy based on histology and, importantly, early assessment of tumor response, as a means of patient enrichment, could be examined in other lung cancer studies. Such an approach might be suitable for trials where there are no predictive biomarkers.

[577]

TÍTULO / TITLE: - Intracellular Poly(I:C) Initiated Gastric Adenocarcinoma Cell Apoptosis and Subsequently Ameliorated NK Cell Functions.

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

REVISTA / JOURNAL: - J Interferon Cytokine Res. 2013 Sep 13.

●● [Enlace al texto completo \(gratis o de pago\) 1089/jir.2012.0118](#)

AUTORES / AUTHORS: - Qu J; Hou Z; Han Q; Jiang W; Zhang C; Tian Z; Zhang J

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Institute of Immunopharmacology and Immunotherapy, Shandong University, Jinan, China .

RESUMEN / SUMMARY: - Natural killer (NK) cells are granular lymphocytic cells that exert essential functions in viral infection defense and tumor immune surveillance. However, the functions of NK cells were impaired in cancer patients. Polycytidylic acid [poly(I:C)] has been used as an immune adjuvant to improve innate and adaptive immune responses. In this study, intracellular poly(I:C) could trigger gastric adenocarcinoma cells apoptosis quickly. Meanwhile, the sensitivity of poly(I:C)-treated gastric adenocarcinoma cells to NK cell cytotoxicity was increased, concomitant with the elevated expression of MICA/B and Fas. Furthermore, the cytotoxic activity of NK cells against tumor cells was augmented significantly by the supernatant from poly(I:C)-transfected tumor cells compared with NK cells treated by the supernatant from untreated tumor cells, as well as the proliferation and migration abilities of NK cells. In this process, the activating receptors and cytotoxic-associated molecules of NK cells were up-regulated. Further investigation showed that type I interferon (IFN) produced by poly(I:C)-transfected gastric adenocarcinoma cells played an important role in this process. Our findings demonstrated that intracellular poly(I:C) not only triggered gastric adenocarcinoma cell apoptosis, but also enhanced NK responses via inducing type I IFN production by gastric adenocarcinoma cells. These functions make poly(I:C) a promising therapeutic medicine for gastric adenocarcinoma.

[578]

TÍTULO / TITLE: - Androgen receptor (AR) positive vs negative roles in prostate cancer cell deaths including apoptosis, anoikis, entosis, necrosis and autophagic cell death.

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

REVISTA / JOURNAL: - Cancer Treat Rev. 2013 Aug 7. pii: S0305-7372(13)00139-4. doi: 10.1016/j.ctrv.2013.07.008.

●● Enlace al texto completo (gratis o de pago) 1016/j.ctrv.2013.07.008

AUTORES / AUTHORS: - Wen S; Niu Y; Lee SO; Chang C

INSTITUCIÓN / INSTITUTION: - Chawnshang Chang Sex Hormone Research Center, Tianjin Institute of Urology, Tianjin Medical University, Tianjin 300211, China; George Whipple Lab for Cancer Research, Departments of Pathology and Urology, University of Rochester Medical Center, Rochester, NY 14642, USA.

RESUMEN / SUMMARY: - Androgen/androgen receptor (AR) signaling plays pivotal roles in the prostate development and homeostasis as well as in the progression of prostate cancer (PCa). Androgen deprivation therapy (ADT) with anti-androgens remains as the main treatment for later stage PCa, and it has been shown to effectively suppress PCa growth during the first 12-24 months. However, ADT eventually fails and tumors may re-grow and progress into the castration resistant stage. Recent reports revealed that AR might play complicated and even opposite roles in PCa progression that might depend on cell types and tumor stages. Importantly, AR may influence PCa progression via differential modulation of various cell deaths including apoptosis, anoikis, entosis, necrosis, and autophagic cell deaths. Targeting AR may induce PCa cell apoptosis, autophagic cell deaths and programmed necrosis, yet targeting AR may suppress cell deaths via anoikis and entosis that may potentially lead to increased metastasis. These differential functions of AR in various types of PCa cell death might challenge the current ADT with anti-androgens treatment. Further detailed dissection of molecular mechanisms by which AR modulates different PCa cell deaths will help us to develop a better therapy to battle PCa.

[579]

TÍTULO / TITLE: - Cyproheptadine-induced myeloma cell apoptosis is associated with inhibition of the PI3K/AKT signaling.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Aug 23. doi: 10.1111/ejh.12193.

●● Enlace al texto completo (gratis o de pago) 1111/ejh.12193

AUTORES / AUTHORS: - Li J; Cao B; Zhou S; Zhu J; Zhang Z; Hou T; Mao X

INSTITUCIÓN / INSTITUTION: - Cyrus Tang Hematology Center, Jiangsu Institute of Hematology, The First Affiliated Hospital, Soochow University, Suzhou, China.

RESUMEN / SUMMARY: - Recent studies revealed that the anti-allergic cyproheptadine displays anti-blood cancer activity. However, its mechanism is still elusive. In the present study, cyproheptadine was found to decrease the expression of anti-apoptotic proteins including Bcl-2, Mcl-1, and XIAP. More importantly, cyproheptadine-induced apoptosis was accompanied by suppression of AKT activation in myeloma cells. In the subsequent study, cyproheptadine was found to inhibit insulin-like growth factor 1-

triggered AKT activation in a time- and concentration-dependent manner. Specifically, cyproheptadine blocked AKT translocation from nuclei for phosphorylation. This inhibition led to suppressed activation of p70S6K and 4EBP1, two key downstream signaling proteins in the PI3K/AKT pathway. However, cyproheptadine did not display inhibition on activation of IGF-1R or STAT3, possible upstream signals of AKT activation. These results further demonstrated that cyproheptadine suppresses the PI3K/AKT signaling pathway, which is probably critical for cyproheptadine-induced MM cell apoptosis. This article is protected by copyright. All rights reserved.

[580]

TÍTULO / TITLE: - Predictive power of quantitative and qualitative fecal immunochemical tests for hemoglobin in population screening for colorectal neoplasm.

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

REVISTA / JOURNAL: - Eur J Cancer Prev. 2013 Aug 11.

●● Enlace al texto completo (gratis o de pago) [1097/CEJ.0b013e328364f229](https://doi.org/10.1097/CEJ.0b013e328364f229)

AUTORES / AUTHORS: - Huang Y; Li Q; Ge W; Cai S; Zhang S; Zheng S

INSTITUCIÓN / INSTITUTION: - aKey Laboratory of Cancer Prevention and Intervention, China National Ministry of Education, Key Laboratory of Molecular Biology in Medical Sciences, Cancer Institute, The Second Affiliated Hospital, Zhejiang University School of Medicine bJiashan Institute of Cancer Prevention and Treatment, Zhejiang Province, China.

RESUMEN / SUMMARY: - The aim of this study was to evaluate the performance of qualitative and quantitative fecal immunochemical tests (FITs) in population screening for colorectal neoplasm. A total of 9000 participants aged between 40 and 74 years were enrolled in this study. Each participant received two stool sampling tubes and was asked to simultaneously submit two stool samples from the same bowel movement. The stool samples of each participant were tested using an immunogold labeling FIT dipstick (qualitative FIT) and an automated fecal blood analyzer (quantitative FIT). Colonoscopy was performed for those who test positive in either FIT. The positive predictive values and population detection rates of the FITs for predicting colorectal neoplasm were compared. A total of 6494 (72.16%) participants simultaneously submitted two stool samples. The diagnostic consistency for a positive result between quantitative and qualitative FITs was poor ($\kappa=0.278$, 95% confidence interval=0.223-0.333). The positive predictive values of the quantitative FIT were significantly higher than those of the qualitative FIT for predicting large (≥ 1 cm) adenomas (23 cases, 14.29% and 16 cases, 6.72%, $P=0.013$) and colorectal cancer (10 cases, 6.21% and 5 cases, 2.10%, $P=0.034$); however, the population detection rate for advanced neoplasm of the quantitative FIT was not significantly different from that of the qualitative FIT. Quantitative FIT is superior to qualitative FIT in predicting advanced

colorectal neoplasm during colorectal cancer screening. Further studies are needed to elucidate the causes of the predictive superiority.

[581]

TÍTULO / TITLE: - The DNA index is a strong predictive marker in intrahepatic cholangiocarcinoma: the results of a five-year prospective study.

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

REVISTA / JOURNAL: - Surg Today. 2013 Aug 24.

●● Enlace al texto completo (gratis o de pago) [1007/s00595-013-0701-7](#)

AUTORES / AUTHORS: - Kamphues C; Al-Abadi N; Durr A; Bova R; Klauschen F; Stenzinger A; Bahra M; Al-Abadi H; Neuhaus P; Seehofer D

INSTITUCIÓN / INSTITUTION: - Department of General Visceral and Transplantation Surgery, Charite University Hospital, Berlin, Germany, carsten.kamphues@charite.de.

RESUMEN / SUMMARY: - PURPOSE: Predictive markers for risk stratification among patients with intrahepatic cholangiocarcinoma (IHC) are still lacking. Therefore, recent studies have focused on identifying the biological aspects of tumors that can provide more information about the tumor aggressiveness. The aim of this study was to prospectively evaluate the prognostic potential of the DNA index in patients undergoing liver resection for IHC. METHODS: In a prospective long-term follow-up study, the DNA index of 65 IHC patients undergoing liver resection was assessed by DNA image cytometry, and this parameter, as well as standard histopathological parameters, correlated with the patient survival. RESULTS: The mean DNA index was 1.69 +/- 0.66 (range, 0.9-4.3). The univariate survival analysis showed that the DNA index (p = 0.024) and tumor stage (p = 0.017) were associated with patient survival, whereas all other standard histopathological factors had no predictive value. The multivariate analysis identified the DNA index (p = 0.050) and tumor stage (p = 0.028) as independent prognostic parameters. CONCLUSIONS: The DNA index is an independent predictive marker for IHC after liver resection. It is superior to most standard histopathological parameters and can be assessed pre- and postoperatively. Therefore, the DNA index might represent a promising tool in the decision-making process for patients with IHC.

[582]

TÍTULO / TITLE: - Evaluation of ABO blood group as a prognostic marker in renal cell carcinoma.

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

REVISTA / JOURNAL: - BJU Int. 2013 Sep 5. doi: 10.1111/bju.12436.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12436](#)

AUTORES / AUTHORS: - de Martino M; Waldert M; Haitel A; Schatzl G; Shariat SF; Klatter T

INSTITUCIÓN / INSTITUTION: - Department of Urology, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - **OBJECTIVE:** To evaluate ABO blood group as a prognostic marker in patients with renal cell carcinoma (RCC). **PATIENTS AND METHODS:** This retrospective study included 556 consecutive patients, who underwent surgery for RCC at a single institution. Associations of ABO blood group with clinical and pathological variables were assessed with Kruskal-Wallis tests and chi-square tests. The impact on overall and RCC-specific survival was analyzed with univariable and multivariable Cox proportional hazards regression models. **RESULTS:** Blood group O was associated with absence of lymph node metastases (P=0.034) and presence of bilateral RCC (P=0.017). No associations with age, gender, body mass index, Charlson's co-morbidity index, T stage, M stage, grade and histological subtype were observed. In univariable and multivariable survival analysis, ABO blood group was not associated with overall and RCC-specific survival. **CONCLUSIONS:** In this study, ABO blood group was not linked with RCC prognosis. Blood group O may be associated with absence of lymph node metastases and presence of bilateral RCC. External validation in larger cohorts is necessary.

[583]

TÍTULO / TITLE: - Monochloramine suppresses the proliferation of colorectal cancer cell line Caco-2 by both apoptosis and G2/M cell cycle arrest.

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

REVISTA / JOURNAL: - Cell Biochem Funct. 2013 Aug 15. doi: 10.1002/cbf.2992.

●● [Enlace al texto completo \(gratis o de pago\) 1002/cbf.2992](#)

AUTORES / AUTHORS: - Kohda T; Sakuma S; Abe M; Fujimoto Y

INSTITUCIÓN / INSTITUTION: - Laboratory of Physiological Chemistry, Osaka University of Pharmaceutical Sciences, Takatsuki, Osaka, Japan.

RESUMEN / SUMMARY: - The aim of this study was to assess a possible role of monochloramine (NH₂Cl), one of the reactive chlorine species, which induce oxidative stress, on the proliferation of colorectal cancer cell line Caco-2. At concentrations ranging from 10 to 200 μM, NH₂Cl (14-61% inhibition), but not hypochlorous acid, dose-dependently inhibited the cell viability of Caco-2 cells. Experiments utilizing methionine (a scavenger of NH₂Cl), taurine-chloramine and glutamine-chloramine revealed that only NH₂Cl affects the cancer cell proliferation among reactive chlorine species, with a relative specificity. Furthermore, flow-cytometry experiments showed that the anti-proliferative effect of NH₂Cl is partially attributable to both apoptosis and G2/M cell cycle arrest. These results suggest that NH₂Cl has the potential to suppress colorectal cancer cell proliferation. Copyright © 2013 John Wiley & Sons, Ltd.

[584]

TÍTULO / TITLE: - MiR-148^a regulates the growth and apoptosis in pancreatic cancer by targeting CCKBR and Bcl-2.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1115-2](#)

AUTORES / AUTHORS: - Zhang R; Li M; Zang W; Chen X; Wang Y; Li P; Du Y; Zhao G; Li L

INSTITUCIÓN / INSTITUTION: - Department of Emergency, The First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe Road, Zhengzhou, Henan, 450052, China.

RESUMEN / SUMMARY: - Our previous studies have revealed that miR-148^a is downregulated in pancreatic cancer. Bioinformatics analysis has shown cholecystokinin-B receptor (CCKBR) and B cell lymphoma (Bcl-2) to be potential targets of miR-148^a. But the pathophysiologic role of miR-148^a and its relevance to the growth and development of pancreatic cancer are yet to be investigated. The purpose of this study is to elucidate the molecular mechanisms where miR-148^a acts as a tumor suppressor in pancreatic cancer. Our results showed significant downregulation of miR-148^a in 28 pancreatic cancer tissue samples and five pancreatic cancer cell lines, compared with their non-tumor counterparts by qRT-PCR. MiR-148^a was found to not only inhibit the proliferation of pancreatic cancer cells (PANC-1 and AsPC-1) in vitro by MTT assay and colony formation assay, but also to promote cells apoptosis in vitro by Annexin V-FITC apoptosis detection and caspase activity assay. Using western blot and luciferase activity assay, CCKBR and Bcl-2 were identified as targets of miR-148^a. Moreover, we also found that the expression of Bcl-2 lacking in 3'UTR could abrogate the pro-apoptosis function of miR-148^a. These findings suggest the importance of miR-148^a's targeting of CCKBR and Bcl-2 in the regulation of pancreatic cancer growth and apoptosis.

[585]

TÍTULO / TITLE: - Expression of Asparagine Synthetase Predicts in vitro Response to L-asparaginase in Canine Lymphoid Cell Lines.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Sep 16.

●● Enlace al texto completo (gratis o de pago) [3109/10428194.2013.842980](#)

AUTORES / AUTHORS: - Smallwood TL; Small GW; Suter SE; Richards KL

RESUMEN / SUMMARY: - Abstract L-asparaginase (L-asp), a bacterial enzyme that depletes extracellular asparagine, is used to treat acute lymphoblastic leukemia in humans and a variety of aggressive lymphoid malignancies in dogs. Resistance to this drug is an important cause of treatment failure in both species. Using canine lymphoid cell lines, we found L-asp sensitivity is strongly negatively correlated with the level of methylation of the asparagine synthetase (ASNS) promoter. Selection for in vitro

resistance was accompanied by increased ASNS promoter methylation and decreased ASNS mRNA expression. In addition, treatment with the hypomethylating agent 5-azacytidine increased resistance to L-asparaginase. ASNS methylation and expression is not predictive of overall survival or progression-free survival in canine lymphoma patients treated with L-asparaginase. Our data suggest that ASNS is an important factor in mediating in vitro response of canine lymphoid cells to L-asparaginase; however, resistance mechanisms may be more complex in dogs treated clinically with L-asparaginase, potentially due to concurrent treatments.

[586]

TÍTULO / TITLE: - Germline genetic variants in ABCB1, ABCC1 and ALDH1A1, and risk of hematological and gastrointestinal toxicities in a SWOG Phase III trial S0221 for breast cancer.

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

REVISTA / JOURNAL: - Pharmacogenomics J. 2013 Sep 3. doi: 10.1038/tpj.2013.32.

- [Enlace al texto completo \(gratuito o de pago\) 1038/tpj.2013.32](#)

AUTORES / AUTHORS: - Yao S; Sucheston LE; Zhao H; Barlow WE; Zirpoli G; Liu S; Moore HC; Thomas Budd G; Hershman DL; Davis W; Ciupak GL; Stewart JA; Isaacs C; Hobday TJ; Salim M; Hortobagyi GN; Gralow JR; Livingston RB; Albain KS; Hayes DF; Ambrosone CB

INSTITUCIÓN / INSTITUTION: - Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA.

RESUMEN / SUMMARY: - Hematological and gastrointestinal toxicities are common among patients treated with cyclophosphamide and doxorubicin for breast cancer. To examine whether single-nucleotide polymorphisms (SNPs) in key pharmacokinetic genes were associated with risk of hematological or gastrointestinal toxicity, we analyzed 78 SNPs in ABCB1, ABCC1 and ALDH1A1 in 882 breast cancer patients enrolled in the SWOG trial S0221 and treated with cyclophosphamide and doxorubicin. A two-SNP haplotype in ALDH1A1 was associated with an increased risk of grade 3 and 4 hematological toxicity (odds ratio=1.44, 95% confidence interval=1.16-1.78), which remained significant after correction for multiple comparisons. In addition, four SNPs in ABCC1 were associated with gastrointestinal toxicity. Our findings provide evidence that SNPs in pharmacokinetic genes may have an impact on the development of chemotherapy-related toxicities. This is a necessary first step toward building a clinical tool that will help assess risk of adverse outcomes before undergoing chemotherapy. The Pharmacogenomics Journal advance online publication, 3 September 2013; doi:10.1038/tpj.2013.32.

[587]

TÍTULO / TITLE: - Evaluation of YO-PRO-1 as an early marker of apoptosis following radiofrequency ablation of colon cancer liver metastases.

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

REVISTA / JOURNAL: - Cytotechnology. 2013 Sep 25.

●● Enlace al texto completo (gratis o de pago) [1007/s10616-013-9565-3](#)

AUTORES / AUTHORS: - Fujisawa S; Romin Y; Barlas A; Petrovic LM; Turkekul M; Fan N; Xu K; Garcia AR; Monette S; Klimstra DS; Erinjeri JP; Solomon SB; Manova-Todorova K; Sofocleous CT

INSTITUCIÓN / INSTITUTION: - Molecular Cytology Core Facility, Memorial Sloan-Kettering Cancer, New York, NY, USA.

RESUMEN / SUMMARY: - Radiofrequency (RF) ablation (RFA) is a minimally invasive treatment for colorectal-cancer liver metastases (CLM) in selected nonsurgical patients. Unlike surgical resection, RFA is not followed by routine pathological examination of the target tumor and the surrounding liver tissue. The aim of this study was the evaluation of apoptotic events after RFA. Specifically, we evaluated YO-PRO-1 (YP1), a green fluorescent DNA marker for cells with compromised plasma membrane, as a potential, early marker of cell death. YP1 was applied on liver tissue adherent on the RF electrode used for CLM ablation, as well as on biopsy samples from the center and the margin of the ablation zone as depicted by dynamic CT immediately after RFA. Normal pig and mouse liver tissues were used for comparison. The same samples were also immunostained for fragmented DNA (TUNEL assay) and for active mitochondria (anti-OxPhos antibody). YP1 was also used simultaneously with propidium iodine (PI) to stain mouse liver and samples from ablated CLM. Following RFA of human CLM, more than 90 % of cells were positive for YP1. In nonablated, dissected pig and mouse liver however, we found similar YP1 signals (93.1 % and 65 %, respectively). In samples of intact mouse liver parenchyma, there was a significantly smaller proportion of YP1 positive cells (22.7 %). YP1 and PI staining was similar for ablated CLM. However in dissected normal mouse liver there was initial YP1 positivity and complete absence of the PI signal and only later there was PI signal. Conclusion: This is the first time that YP1 was applied in liver parenchymal tissue (rather than cell culture). The results suggest that YP1 is a very sensitive marker of early cellular events reflecting an early and widespread plasma membrane injury that allows YP1 penetration into the cells.

[588]

TÍTULO / TITLE: - Ursolic acid inhibits tumor angiogenesis and induces apoptosis through mitochondrial-dependent pathway in Ehrlich ascites carcinoma tumor.

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

REVISTA / JOURNAL: - Chem Biol Interact. 2013 Sep 17. pii: S0009-2797(13)00229-9. doi: 10.1016/j.cbi.2013.09.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.09.004](#)

AUTORES / AUTHORS: - Saraswati S; Agrawal SS; Alhaider AA

INSTITUCIÓN / INSTITUTION: - Camel Biomedical Research Unit, College of Pharmacy and Medicine, King Saud University, Riyadh, Saudi Arabia. Electronic address: saritasaraswati@gmail.com.

RESUMEN / SUMMARY: - Ursolic acid (UA) is a pentacyclic triterpene naturally occurring in many plant foods. In the present study, we investigated anti-cancer activity of UA in vivo in Ehrlich ascites carcinoma (EAC) tumor. 15x10⁶ EAC cells were implanted intraperitoneally (i.p., ascitic tumor) and subcutaneous (s.c., solid tumor) in Swiss albino mice. Mice with established tumors received UA i.p. at 25, 50 and 100mg/kg bw for 14d in ascitic and 100mg/kg bw in solid tumor for 30d. On day 15, blood samples were collected for hematological assessment of hemoglobin (Hb%), RBCs, WBCs and PCV. Tumor volume, cell viability, angiogenic, anti-angiogenic, anti-inflammatory factors and antioxidant parameters were determined. Immunohistochemistry analysis for VEGF, iNOS, CD31, caspase-3 and Bax were also performed. UA significantly inhibited tumor growth, cell viability, in both ascites and solid tumor model in vivo (p<0.001). The anti-angiogenic effects were accompanied with decreased VEGF, iNOS, TNF-alpha and increased IL-12 levels. UA at 100mg/kg bw dose significantly increased SOD and CAT activity (p<0.01). GSH and TBARS were increased as compared to control group (p<0.001). Furthermore, UA increased total RBCs, WBCs as well as Hb% significantly (p<0.05) compared to cyclophosphamide (CP). Histopathological examination of tumor cells in the treated group demonstrated signs of apoptosis with chromatin condensation and cell shrinkage. Decreased peritoneal angiogenesis showed the anti-angiogenic potential. UA downregulated VEGF & iNOS expression whereas bax and caspase-3 expressions were upregulated suggesting drug induced tumor cell apoptosis through activating the pro-apoptotic bcl-2 family and caspase-3 and downregulation of VEGF. The present study sheds light on the potent antitumor property of the UA and can be extended further to develop therapeutic protocols for treatment of cancer.

[589]

TÍTULO / TITLE: - Predicting response to the anti-estrogen fulvestrant in recurrent ovarian cancer.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Jul 30. pii: S0090-8258(13)01019-6. doi: 10.1016/j.ygyno.2013.07.099.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ygyno.2013.07.099](#)

AUTORES / AUTHORS: - Argenta PA; Um I; Kay C; Harrison D; Faratian D; Sueblinvong T; Geller MA; Langdon SP

INSTITUCIÓN / INSTITUTION: - Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Minnesota, Minneapolis, MN, USA. Electronic address: argenta@umn.edu.

RESUMEN / SUMMARY: - BACKGROUND: Anti-estrogen therapy appears to have efficacy in a subset of ovarian cancers, as demonstrated in multiple phase II studies. Identifying sensitive patients early in treatment may allow for targeted, low-toxicity primary therapy or prevention of recurrence. We have previously demonstrated that the likelihood of response to letrozole could be improved by patient selection based on estrogen-pathway marker expression. We sought to identify ovarian cancer biomarkers that might indicate sensitivity to fulvestrant, an estrogen receptor antagonist. METHODS: Tissue samples from the primary tumors of patients enrolled in a phase II study of fulvestrant for the treatment of multiply-recurrent ovarian cancer were embedded randomly in a tissue microarray (TMA). Estrogen receptor alpha (ERalpha) expression was assessed by both conventional immunohistochemistry (IHC) and quantitative immunofluorescence (IF) (AQUA) while expression of 14 other estrogen-regulated markers was assessed by quantitative IF and correlated with clinical outcomes. RESULTS: Almost half of patients experienced clinical benefit (CR+PR+SD) at 90days despite a median of 5 previous treatment regimens. 24 of 26 patient samples were available and included in the TMA. ERalpha expression, measured either by conventional IHC or by AQUA analysis, was associated with clinical benefit, while TFF1 and vimentin expression (measured by IF AQUA score) was predictive of progression-free survival. CONCLUSIONS: These results confirm our previous observation that clinical ovarian cancer includes a subset of tumors with sensitivity to estrogen pathway blockade. Expression profile of sensitive tumors appears to be detectably different from insensitive tumors, suggesting that further improvements in treatment efficacy can be obtained through appropriate patient selection.

[590]

TÍTULO / TITLE: - Saponin B, a novel cytostatic compound purified from *Anemone taipaiensis*, induces apoptosis in a human glioblastoma cell line.

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

REVISTA / JOURNAL: - Int J Mol Med. 2013 Nov;32(5):1077-84. doi: 10.3892/ijmm.2013.1500. Epub 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1500](http://dx.doi.org/10.3892/ijmm.2013.1500)

AUTORES / AUTHORS: - Wang Y; Tang H; Zhang Y; Li J; Li B; Gao Z; Wang X; Cheng G; Fei Z

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Xijing Institute of Clinical Neuroscience, Xijing Hospital, Fourth Military Medical University, Xi'an, Shannxi, P.R. China.

RESUMEN / SUMMARY: - Glioblastoma multiforme (GBM) is one of the most common malignant brain tumors. Saponin B, a novel compound isolated from the medicinal plant, *Anemone taipaiensis*, has been found to have a strong time- and dose-dependent cytostatic effect on human glioma cells and to suppress the growth of U87MG GBM cells. In this study, we investigated whether saponin B induces the apoptosis of glioblastoma cells and examined the underlying mechanism(s) of action of saponin B. Saponin B significantly suppressed U87MG cell proliferation. Flow cytometric analysis of DNA in the U87MG cells confirmed that saponin B blocked the cell cycle at the S phase. Furthermore, treatment of the U87MG cells with saponin B induced chromatin condensation and led to the formation of apoptotic bodies, as observed under a fluorescence microscope, and Annexin V/PI assay further suggested that phosphatidylserine (PS) externalization was apparent at higher drug concentrations. Treatment with saponin B activated the receptor-mediated pathway of apoptosis, as western blot analysis revealed the activation of Fas-I. Saponin B increased the Bax and caspase-3 ratio and decreased the protein expression of Bcl-2. The results from the present study demonstrate that the novel compound, saponin B, effectively induces the apoptosis of GBM cells and inhibits glioma cell growth and survival. Therefore, saponin B may be a potential candidate for the development of novel cancer therapeutics with antitumor activity against gliomas.

[591]

TÍTULO / TITLE: - Prognostic Value of Hepatocyte Nuclear Factors 4alpha and 1alpha Identified by Tissue Microarray in Resectable Hepatocellular Carcinoma.

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

REVISTA / JOURNAL: - J Gastroenterol Hepatol. 2013 Aug 23. doi: 10.1111/jgh.12371.

●● [Enlace al texto completo \(gratis o de pago\) 1111/jgh.12371](#)

AUTORES / AUTHORS: - Shim JH; Kang HJ; Han S; Lee YJ; Lee SG; Yu E; Lee HC

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND AND AIM: This study aimed to investigate the prognostic value of expression of hepatocyte nuclear factors (HNFs) involved in hepatic gene transcription in patients undergoing curative resection for hepatocellular carcinoma (HCC). METHODS: We performed immunohistochemical analyses on microarrays of the tumors and matched adjacent tissue using antibodies against HNF1alpha, HNF1beta, HNF4alpha, and alpha-fetoprotein (AFP). We evaluated the prognostic value of biomarker expression using Cox regression and the Kaplan-Meier method in a training cohort of 220 patients, and conducted an independent validation in 232 patients. We also determined whether measurement of HNFs improved risk prediction beyond the use of established factors, using net reclassification

improvement (NRI). RESULTS: Post-surgical recurrence and hepatic death were predicted by intratumoral HNF4alpha underexpression in both cohorts. In the training cohort they were also predicted by peritumoral HNF1alpha positivity. A pooled cohort analysis showed that these predictors were independently associated with early but not late phase recurrence, and resultant mortality. Intratumoral expression levels of HNF4alpha were correlated with those of HNF1alpha, HNF1beta, and AFP (P<0.05). Similarly HNF1alpha expression in peritumoral tissue was correlated with that of other markers (P<0.05). There was no significant correlation between expression of HNF4alpha in tumors and HNF1alpha in peritumoral tissue. Adding combinations of intratumoral HNF4alpha and peritumoral HNF1alpha to 2-year recurrence and 5-year mortality models including known clinicopathological prognostic factors significantly improved the NRI indexes (39% and 44%, respectively; P<0.05). CONCLUSIONS: Immunohistological activation of intratumoral HNF4alpha and depletion of peritumoral HNF1alpha have prognostic significance for delayed recurrence and death after HCC resection.

[592]

TÍTULO / TITLE: - Silencing tankyrase and telomerase promotes A549 human lung adenocarcinoma cell apoptosis and inhibits proliferation.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Oct;30(4):1745-52. doi: 10.3892/or.2013.2665. Epub 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2665](#)

AUTORES / AUTHORS: - Lu H; Lei Z; Lu Z; Lu Q; Lu C; Chen W; Wang C; Tang Q; Kong Q

INSTITUCIÓN / INSTITUTION: - Department of Oncology, the Central Hospital of Wuhan, Wuhan, Hubei, P.R. China.

RESUMEN / SUMMARY: - Telomeres are the end structures of chromosomes in mammalian cells; they play a pivotal role in maintaining the stability of the chromosome and become shorter with each cell division. However, several types of tumor cells express telomerase in very high levels to overcome this crisis and achieve the ability to proliferate endlessly. The telomerase inhibitors can partly inhibit tumor cell proliferation and promote apoptosis, but their roles are only limited. Tankyrase is a poly(ADP-ribose) polymerase which has synergistic effect on telomerase, and is expressed in lung cancer cells in high levels. In the present study, antisense oligonucleotides of telomerase (ashTERT) and tankyrase (asTANKS) were used as specific inhibitors to silence the expression of target genes in A549 human lung adenocarcinoma cells by transfection. The results showed that ashTERT and asTANKS suppressed the expression of telomerase and tankyrase significantly; both inhibited the activity of telomerase and the combination group achieved better effect, but only ashTERT shortened the length of telomeres, asTANKS did not. Further studies showed

that ashTERT and asTANKS-promoted A549 apoptosis was not mediated by downregulation of the expression of the antiapoptotic gene BCL-2 or upregulation of the expression of the proapoptotic gene BAX, but by adjusting the two isoforms proportion of myeloid cell leukemia-1 (MCL1) which can interact with tankyrase directly. MCL-1short (MCL1S), a pro-apoptotic gene, increased more than MCL-1Long (MCL1L) which is an anti-apoptotic gene, leading to A549 cell apoptosis and a similar result was obtained in nude mice in vivo. The present study suggests that combination of the inhibitors of telomerase and tankyrase can be used as a strategy for the treatment of lung cancer in humans.

[593]

TÍTULO / TITLE: - Antitumor enhancement by adoptive transfer of tumor antigen primed, inactivated MHC-haploidentical lymphocytes.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Sep 14. pii: S0304-3835(13)00656-3. doi: 10.1016/j.canlet.2013.09.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.canlet.2013.09.003](#)

AUTORES / AUTHORS: - Shi G; Zhou C; Wang D; Ma W; Liu B; Zhang S

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Cancer Institute, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100021, China.

RESUMEN / SUMMARY: - The present study investigated the antitumor effects by adoptive transfer of tumor antigen primed, inactivated MHC-haploidentical lymphocytes in TC-1 lung cancer mouse model. Our studies revealed that the inactivated MHC-haploidentical effector cells display the antitumor activity in vitro and target the tumor in vivo. After adoptive transferring these effector cells, the Th1 cytokines such as IL-2 and IFN-gamma are elevated in the serum; the recipient tumor-specific cytotoxic T-cells and natural killer cells are activated; tumor specific memory T cells are induced; tumor growth is inhibited and mouse survival is prolonged. The results indicate that MHC-haploidentical lymphocytes provide both effector cells which can target the tumor cells through the identical MHC molecules and an adjuvant effects through the unmatched allogeneic MHC molecules which induces endogenous innate and adaptive antitumor immune responses.

[594]

TÍTULO / TITLE: - Anti-cancer effect and apoptosis induction of cordycepin through DR3 pathway in the human colonic cancer cell HT-29.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Oct;60:439-47. doi: 10.1016/j.fct.2013.07.068. Epub 2013 Aug 11.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.07.068](https://doi.org/10.1016/j.fct.2013.07.068)

AUTORES / AUTHORS: - Lee SY; Debnath T; Kim SK; Lim BO

INSTITUCIÓN / INSTITUTION: - Department of Applied Biochemistry, College of Biomedical & Health Science, Konkuk University, Chungju, Republic of Korea.

RESUMEN / SUMMARY: - Cordycepin is known to have many pharmacological effects such as anti-tumorigenic, anti-inflammatory and anti-angiogenic activity. However, cordycepin induced apoptosis through the DR3 pathway in human colon cancer cells has not been studied. The effect of cordycepin on anti-proliferation was investigated in this study. Cordycepin significantly inhibited cell viability in a dose and time-dependent manner. Cordycepin increased sub G1 and G2/M phase arrest on HT-29 cells at the concentration of 100µM, whereas cordycepin at 200µM and 400µM increased G1 phase arrest. Cordycepin induced apoptosis in HT-29 cells in a dose-dependent manner as detected by Hoechst and Annexin V-FITC staining. Intracellular ROS levels were higher in cordycepin treated cells as compared to control cells. The protein related to apoptosis was determined by antibody array. p53 and Bax expression increased treatment with cordycepin for 18h. DR3, caspase-8, caspase-1, cleaved caspase-3 and cleaved PARP expression increased. These findings suggest that the cordycepin induces apoptosis through the DR3 pathway in human colon cancer HT-29. These findings suggest that cordycepin should be evaluated further as a therapeutic agent in human colon cancer.

[595]

TÍTULO / TITLE: - Dealcoholated red wine induces autophagic and apoptotic cell death in an osteosarcoma cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1016/j.fct.2013.07.078)

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Oct;60:377-84. doi: 10.1016/j.fct.2013.07.078. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.07.078](https://doi.org/10.1016/j.fct.2013.07.078)

AUTORES / AUTHORS: - Tedesco I; Russo M; Bilotto S; Spagnuolo C; Scognamiglio A; Palumbo R; Nappo A; Iacomino G; Moio L; Russo GL

INSTITUCIÓN / INSTITUTION: - Istituto Scienze dell'Alimentazione, Consiglio Nazionale delle Ricerche, 83100 Avellino, Italy.

RESUMEN / SUMMARY: - Until recently, the supposed preventive effects of red wine against cardiovascular diseases, the so-called "French Paradox", has been associated to its antioxidant properties. The interest in the anticancer capacity of polyphenols present in red wine strongly increased consequently to the enormous number of studies on resveratrol. In this study, using lyophilized red wine, we present evidence that its anticancer effect in a cellular model is mediated by apoptotic and autophagic cell death. Using a human osteosarcoma cell line, U2Os, we found that the lyophilized red wine was cytotoxic in a dose-dependent manner with a maximum effect in the

range of 100-200µg/ml equivalents of gallic acid. A mixed phenotype of types I/II cell death was evidenced by means of specific assays following treatment of U2Os with lyophilized red wine, e.g., autophagy and apoptosis. We found that cell death induced by lyophilized red wine proceeded through a mechanism independent from its anti-oxidant activity and involving the inhibition of PI3K/Akt kinase signaling. Considering the relative low concentration of each single bioactive compound in lyophilized red wine, our study suggests the activation of synergistic mechanism able to inhibit growth in malignant cells.

[596]

TÍTULO / TITLE: - Expression of Biologically Active Human Recombinant Interferon Alpha 2b in Human Breast Cancer Cell Line Bcap-37.

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

REVISTA / JOURNAL: - Appl Biochem Biotechnol. 2013 Aug 23.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12010-013-0420-y](#)

AUTORES / AUTHORS: - Li H; Li X; Liu Q; Shi Z; Shi D

INSTITUCIÓN / INSTITUTION: - Institute of Animal Science, Jiangsu Academy of Agricultural Sciences, Nanjing, 210014, China.

RESUMEN / SUMMARY: - Human interferon alpha 2b (IFNalpha-2b) is a pleiotropic cytokine used to treat various viral diseases and cancers. Conventionally, recombinant human IFNalpha-2b used in clinics was produced by prokaryotic expression system, which always lack of enough biological activity due to limitations on proper folding and post-translational modifications, so the eukaryotic expression system are becoming prevailing method for the production of recombinant proteins. In this study, human breast cancer cell Bcap-37 was firstly used as host for the expression of human IFNalpha-2b, with the expression vector pIRES2-IFN-EGFP, in which IFNalpha-2b gene is under the control of CMV promoter. The expression of recombinant IFNalpha-2b was detected by Western blot and ELISA. Results showed that the concentration of the secreted recombinant IFNalpha-2b in culture medium was 435.7 pg/mL/24 h. Biological activity of the recombinant IFNalpha-2b was assayed by detecting the expression of IFN-inducible genes, including MxA, OAS, PKR, and Caspase1 through QRT-PCR. Results demonstrated that recombinant IFNalpha-2b possess the biological activities. Compared to non-transgenic cells, the expression levels of the aforementioned four IFN-inducible genes were increased by 18.098-, 1.843-, 2.21-, and 3.066-folds, respectively. We got to a conclusion that the human breast cancer cell Bcap-37 could express bioactive recombinant IFNalpha-2b.

[597]

TÍTULO / TITLE: - The prognostic impact of tumor-associated macrophages and intra-tumoral apoptosis in non-small cell lung cancer.

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

REVISTA / JOURNAL: - Histol Histopathol. 2013 Aug 13.

AUTORES / AUTHORS: - Becker M; Muller CB; De Bastiani MA; Klamt F

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, ICBS/UFRGS, and National Institutes for Science and Technology - Translational Medicine (INCT-TM), Porto Alegre (RS), Brazil.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer-related deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung malignancies. Tumor-associated macrophages (TAM) are abundant components of NSCLC. Although under certain conditions TAM can kill tumor cells, they can also act as tumor promoters secreting a variety of factors that directly stimulate tumor invasion and metastasis. TAM presents two distinct phenotypes: the classically activated (or M1) phenotype, which is highly pro-inflammatory (phagocytic and cytotoxic), and the alternatively activated (or M2) phenotype, which has anti-inflammatory and pro-tumoral properties. The polarization status of TAM depends on stimulating factors from the tumor microenvironment, and some in vitro evidence implies that the phagocytosis of apoptotic bodies derived from tumoral cells is a key factor in M1/M2 modulation, raising the question of whether the evaluation of the apoptotic index (AI) and macrophage polarization have a prognostic role in NSCLC patient survival. The present article systematically reviewed the published series of clinical data that correlated the AI and/or macrophage densities and polarization status (M1/M2) with the outcome of non-small cell lung cancer patients. Even though an overwhelming body of clinical data support that TAM's density, micro-anatomical localization, phenotype and intra-tumoral AI are independent predictors of survival time, no study to date has been conducted to evaluate the impact of these parameters altogether in NSCLC patient outcome. Joint analysis of these biologic factors in future studies might reveal their prognostic value in the management of NSCLC cases.

[598]

TÍTULO / TITLE: - Putative prognostic epithelial-to-mesenchymal transition biomarkers for aggressive prostate cancer.

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

REVISTA / JOURNAL: - Exp Mol Pathol. 2013 Oct;95(2):220-226. doi: 10.1016/j.yexmp.2013.07.010. Epub 2013 Aug 6.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.yexmp.2013.07.010](#)

AUTORES / AUTHORS: - Whiteland H; Spencer-Harty S; Thomas DH; Davies C; Morgan C; Kynaston H; Bose P; Fenn N; Lewis PD; Bodger O; Jenkins S; Doak SH

INSTITUCIÓN / INSTITUTION: - College of Medicine, Swansea University, Swansea SA2 8PP, Wales, UK.

RESUMEN / SUMMARY: - Prostate cancer is the second most frequently diagnosed cancer worldwide and is the sixth leading cause of cancer deaths in men, yet it varies greatly in its aggressiveness. Currently, it is not possible to adequately differentiate between patients whose tumors will remain indolent and those patients whose disease will progress, resulting in unnecessary aggressive treatment. Consequently, there is an urgent need to identify markers of prostate cancer progression, invasiveness and metastasis to more accurately predict prognosis. The aim of this study was to assess the ability of key epithelial-to-mesenchymal transition molecules in identifying prostate cancer patients who are likely to develop aggressive tumors. Using 215 archival patient tissue samples, immunohistochemistry was applied to examine the expression and sub-cellular localization of E-Cadherin, Snail, Slug, Twist, Vimentin, BMP-2 and BMP-7. Of the seven markers assessed, a significantly increased expression of Snail protein was observed within the nucleus of prostate cancer cells and was strongly associated with increasing Gleason score and clinical stage. In addition, loss of E-Cadherin expression at the cellular membrane of prostate cancer cells was also significantly associated with increasing Gleason score, clinical stage, and additionally, a reduction in survival.

[599]

TÍTULO / TITLE: - Sorafenib plus dacarbazine in solid tumors: a phase I study with dynamic contrast-enhanced ultrasonography and genomic analysis of sequential tumor biopsy samples.

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

REVISTA / JOURNAL: - Invest New Drugs. 2013 Aug 27.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10637-013-9993-0](#)

AUTORES / AUTHORS: - Lazar V; Lassau N; Meurice G; Lorient Y; Pena C; Massard C; Robert C; Robert T; Le Berre MA; de Baere T; Dessen P; Soria JC; Armand JP

INSTITUCIÓN / INSTITUTION: - Department of Functional Genomics, Institut Gustave Roussy, University Paris-Sud, Villejuif, France, vladimir.lazar@igr.fr.

RESUMEN / SUMMARY: - Purpose Improved prognostic accuracy for treatment response and a wider understanding of drug effects in humans are crucial for enhancing the utility of sorafenib and other promising targeted therapies. We developed a strategy of global genomic investigation of sequential tumor biopsy samples at baseline and 21 days post treatment, and applied this approach in a phase I study of sorafenib plus dacarbazine in patients with solid tumors. The objective of this study was also to validate functional parameters of DCE-US as surrogate markers to predict earlier response. Experimental design Patients received 21-day cycles of oral sorafenib, 400 mg twice daily and dacarbazine, 1,000 mg/m² in a 1-h intravenous infusion on day 1.

Efficacy was assessed using response evaluation criteria in solid tumors. Sequential biopsy samples (baseline and day 21) were obtained from the same tumor. Changes from baseline in global gene expression (GE) measured by genomic microarrays and in tumor vascularity at baseline, D8, D21, D 42 and every 2 cycles using dynamic contrast-enhanced ultrasonography (DCE-US) were analyzed for patients with and without a clinical response to treatment at 3 months. Results Among 23 patients evaluable for treatment efficacy, 17 were eligible for gene expression and DCE-US analyses. One patient achieved a partial response; 14 exhibited stable disease. Ten patients were defined as exhibiting stable disease (SD) and 7, progressive disease (PD) at 3 months. Genomic analyses identified a 237-gene signature that distinguished SD from PD at 3 months. Of note, CDK4 overexpression and PDGFR downregulation were associated with PD. Functional parameters of DCE-US representing the blood volume at baseline, day 8, and day 21 were correlated with disease progression at 3 months. Conclusions This novel approach of sequential investigations in a phase I trial was feasible, detecting early changes in gene expression and tumor vascularity evaluated using DCE-US that may be predictive of clinical outcome.

[600]

TÍTULO / TITLE: - Experimental hypothyroidism increases apoptosis in dimethylbenzanthracene-induced mammary tumors.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Oct;30(4):1651-60. doi: 10.3892/or.2013.2648. Epub 2013 Aug 1.

●● [Enlace al texto completo \(gratuito o de pago\) 3892/or.2013.2648](#)

AUTORES / AUTHORS: - Lopez-Fontana CM; Sasso CV; Maselli ME; Santiano FE; Semino SN; Cuello Carrion FD; Jahn GA; Caron RW

INSTITUCIÓN / INSTITUTION: - Institute of Medicine and Experimental Biology of Cuyo, CONICET, CCT-Mendoza, Mendoza, Argentina.

RESUMEN / SUMMARY: - Epidemiological and in vitro data have not provided conclusive evidence concerning the involvement of thyroid hormones (THs) on mammary carcinogenesis. We used an in vivo model to assess the relationship between THs, adipose tissue and breast cancer development. Female SpragueDawley rats were treated with a dose of 7,12-dimethylbenz(a)anthracene (15 mg/rat) at 55 days of age and were then divided into four experimental groups: hypothyroid rats (HypoT, 0.01% 6-N-propyl-2-thiouracil in drinking water), untreated control (EUT); hyperthyroid rats (HyperT, 0.25 mg/kg/day T4 s.c.) and vehicle-treated control rats. The latency of tumor appearance and the incidence and progression of tumors were determined. At sacrifice, blood samples were collected for hormone determinations and samples of tumor and mammary glands were obtained for immunohistological studies. HypoT rats had retarded growth and an increase in mammary fat. The latency was longer

($p < 0.0001$), the incidence rate was lower ($p < 0.05$) and tumor growth was slower in HypoT rats compared to EUT and HyperT rats. Mitotic index and PCNA immunostaining were similar in all groups. HypoT rats showed increased apoptosis ($p < 0.05$) as evaluated by the apoptotic index and TUNEL staining. No differences in serum prolactin and progesterone were observed. However, circulating estradiol (E2) was significantly lower in HypoT and HyperT rats. Serum leptin levels were reduced in HypoT rats even though the abdominal fat mass was similar in all groups. To note, the leptin level was higher in HypoT rats that developed mammary tumors than the level in non-tumoral HypoT rats. In conclusion, hypothyroidism altered animal growth, breast morphology, body composition, leptin secretion and serum E2 enhancing apoptosis and, consequently, retarding mammary carcinogenesis in rats.

[601]

TÍTULO / TITLE: - Antitumor effects of telomerase-specific replication-selective oncolytic viruses for adenoid cystic carcinoma cell lines.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Sep 19. doi: 10.3892/or.2013.2738.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2738](#)

AUTORES / AUTHORS: - Sato D; Kurihara Y; Kondo S; Urata Y; Fujiwara T; Shintani S

RESUMEN / SUMMARY: - We evaluated the antitumor effect of a telomerase-specific replication-selective adenovirus (Telomelysin, OBP-301) for adenoid cystic carcinoma (ACC) in vitro and in vivo. Adenovirus E1 gene expression was controlled by human telomerase reverse transcription (hTERT). Infection of ACC cells by OBP-301 induced high E1A mRNA expression and subsequent oncolytic cell death in a dose-dependent manner. Using OBP-401 (TelomeScan), a genetically engineered adenovirus that carries the GFP gene under the control of the cytomegalovirus (CMV) promoter at the deleted E3 region of OBP-301, ACC cells expressed bright GFP fluorescence as early as 12 h after OBP-401 infection. The fluorescence intensity gradually increased in a time-dependent manner, followed by rapid cell death due to the cytopathic effect of OBP-401, as evidenced by the floating, highly light-refractive cells using phase-contrast microscopy. Effects of intratumorally injected OBP-401 against established Acc2 xenograft tumors were seen in BALB/c nu/nu mice. The levels of GFP expression following ex vivo infection of OBP-401 may be of value as a positive predictive marker for the outcome of telomerase-specific virotherapy. Our data clearly indicated that telomerase-specific oncolytic adenoviruses have significant therapeutic potential against human ACC in vitro and in vivo. These results suggest that treatment with OBP-301 and OBP-401 may improve the quality of life of oral cancer patients.

[602]

TÍTULO / TITLE: - Sustained-release protamine sulphate-impregnated microspheres may reduce the frequent administration of recombinant interferon alpha-2b in ovarian cancer: in-vitro characterization.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Sep 18.

- Enlace al texto completo (gratis o de pago)

[1097/CAD.0000000000000026](#)

AUTORES / AUTHORS: - Gulia M; Rai S; Jain UK; Katare OP; Katyal A; Madan J

INSTITUCIÓN / INSTITUTION: - aDepartment of Pharmaceutics, Chandigarh College of Pharmacy, Mohali, Panjab bDr. B.R. Ambedkar Centre for Biomedical Research, University of Delhi, Delhi cUniversity Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India.

RESUMEN / SUMMARY: - Parenteral administration of recombinant interferon-alpha-2b (rINF-alpha-2b) at a dose of 50x10 IU once a week for 8 weeks is recommended for ovarian cancer. However, short half-life, small therapeutic index and proteolytic degradation cause fluctuations in plasma level and pose barriers in the development of a clinically viable dosage form. Therefore, in the present investigation, fluorescein isothiocyanate-tagged rINF-alpha-2b was loaded into stearic acid (*rINF-alpha-2b-SMs), pectin (*rINF-alpha-2b-PMs) and gelatin (*rINF-alpha-2b-GMs) microspheres. Parameters such as particle size, zeta potential, encapsulation efficiency and in-vitro release were studied to follow the optimization process. The formulation, *rINF-alpha-2b-GMs of particle size 8.3+/-2.1 µm with an encapsulation efficiency of 76.0+/-7.4%, offered 97.4% of *rINF-alpha-2b release at 288 h. Thus, negatively charged extended-release formulation *rINF-alpha-2b-GMs was then tethered with a gradient concentration (5-20 mg/ml) of a cationic arginine-rich protein stabilizer, protamine sulphate (Pt). The nanoformulation, *rINF-alpha-2b-Pt-GMs-15 superimposed with 15 mg/ml of Pt, released 95.0% of *rINF-alpha-2b at 336 h and was designated as the optimized formulation. The optimized formulation also conserved the primary and secondary structure of *rINF-alpha-2b as analysed by gel electrophoresis and circular dichroism. Moreover, in-vitro cytotoxicity analysis of SKOV3 cells of the optimized nanoformulation reported significantly (one-way analysis of variance test, P<0.05) lower IC50 (414.3 IU/ml) compared with *rINF-alpha-2b-GMs (514.3 IU/ml) and pure rINF-alpha-2b (628.6 IU/ml) at 72 h by offering a prolonged cytotoxic effect. Therefore, *rINF-alpha-2b-Pt-GMs-15, a promising nanomedicine, warrants further in-depth in-vivo study to scale up the technology for clinical translation.

[603]

TÍTULO / TITLE: - Biomarkers and prognosis after r0 resection of colorectal liver metastases.

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

REVISTA / JOURNAL: - Hepatogastroenterology. 2013 Aug;60(126):1469-75. doi: 10.5754/hge12215.

●● Enlace al texto completo (gratis o de pago) [5754/hge12215](https://doi.org/10.5754/hge12215)

AUTORES / AUTHORS: - Radais F; Zaanan A; Lef JH; Flejou JF; Balladur P; Paye F; Tiret E; Duva A; Praz F; Parc Y

RESUMEN / SUMMARY: - Background: Evaluation of biomarkers and clinical factors associated with cancer-specific survival after curative resection for colorectal cancer liver metastases (LM). Methodology: All patients who had an R0 resection for LM between 2000-2006 were reviewed. Clinical and histological data were assessed; p53 expression was studied by IHC. ERCC1 codon 118 and XRCC1 codon 399 were analyzed by PCR-RFLP using BsrDI and HpaII, respectively. Results: Out of 119 patients included (80 synchronous LM (67.2%), median number 2 (1-18)), 104 patients (87.4%) received chemotherapy before recurrence; 60 patients (50.4%) had a p53 negative tumor. ERCC1 distribution was: 31(26%) AAC/AAC, 44(37%) AAC/AAT and 44(37%) AAT/AAT. XRCC1 distribution was: 46(39%) CGG/CGG, 53(44.9%) CGG/CAG and 19(16.1%) CAG/CAG. Three and 5-years disease free survival (DFS) and overall survival (OS) were 31%, 22.7%, 77.4%, and 66.6%, respectively. Node ratio >0.2 (p = 0.0042), LM number >3 (p <0.0001), bilobar localization (p = 0.0074) and preoperative chemotherapy (p = 0.0036) were associated with a shorter DFS. None of the biomarkers was found to influence DFS. In multivariate analysis, a number of LM >3 was the only independent factor. No factor was found to influence OS. Conclusions: The studied biomarkers had no significant impact on prognosis. For routine practice, clinical factors remain the only usable available tools.

[604]

TÍTULO / TITLE: - A semisynthetic taxane Yg-3-46^a effectively evades P-glycoprotein and beta-III tubulin mediated tumor drug resistance in vitro.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Aug 11. pii: S0304-3835(13)00585-5. doi: 10.1016/j.canlet.2013.08.010.

AUTORES / AUTHORS: - Cai P; Lu P; Sharom FJ; Fang WS

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, 2^a Nan Wei Road, Beijing 100050, China.

RESUMEN / SUMMARY: - Tumor resistance, especially that mediated by P-glycoprotein (P-gp) and beta-III tubulin, is a major obstacle to the efficacy of most microtubule-targeting anticancer drugs in clinics. A novel semisynthetic taxane, 2-debenzoyl-2-(3-azidobenzyl)-10-propionyl docetaxel (Yg-3-46^a) was shown to be highly cytotoxic to breast cancer cell lines MCF-7 and MCF/ADR which overexpressed P-gp via long term culture with doxorubicin, and cervical cancer cell lines HeLa and HeLa/betaIII which

overexpressed betaIII-tubulin via stable transfection with TUBB3 gene. siRNA transfection experiments also confirmed that Yg-3-46^a can circumvent P-gp and beta-III tubulin mediated drug resistance. In addition, its cytotoxicity was lower than that of paclitaxel in the human mammary cell line HBL-100 and the human telomerase-immortalized retinal pigment epithelium cell line (hTERT-RPE1), suggesting a better safety margin for this compound in vivo. It exhibited more potent microtubule polymerization ability than paclitaxel in vitro, and also induced G2/M phase arrest in MCF-7/ADR cells. Moreover, it was found to induce apoptosis in MCF-7/ADR cells through the caspase-dependent death-receptor pathway by enhancing levels of Fas and FasL, and activating caspase-8 and 3. Yg-3-46^a was found to be a poorer substrate of P-gp compared to paclitaxel, in both binding and ATPase experiments, which is likely responsible for its ability to circumvent P-gp mediated multidrug resistance (MDR). All of these results indicate that Yg-3-46^a is a novel microtubule-stabilizing agent that has the potential to evade drug resistance mediated by P-gp and beta-III tubulin overexpression.

[605]

TÍTULO / TITLE: - The antimelanoma activity of the histone deacetylase inhibitor panobinostat (LBH589) is mediated by direct tumor cytotoxicity and increased tumor immunogenicity.

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

REVISTA / JOURNAL: - Melanoma Res. 2013 Aug 19.

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

[1097/CMR.0b013e328364c0ed](#)

AUTORES / AUTHORS: - Woods DM; Woan K; Cheng F; Wang H; Perez-Villaruel P; Lee C; Lienlaf M; Atadja P; Seto E; Weber J; Sotomayor EM; Villagra A

INSTITUCIÓN / INSTITUTION: - Departments of aImmunology bMalignant Hematology cMolecular Oncology, H. Lee Moffitt Cancer and Research Institute dDepartment of Cutaneous Oncology and the Donald A. Adam Comprehensive Melanoma Research Center, H. Lee Moffitt Cancer and Research Institute eDepartment of Molecular Medicine, Morsani College of Medicine, Tampa fCollege of Medicine at the University of South Florida, Gainesville, Florida gNovartis Pharmaceuticals, East Hanover, New Jersey, USA.

RESUMEN / SUMMARY: - Melanoma is the deadliest skin cancer, and its incidence has been increasing faster than any other cancer. Although immunogenic, melanoma is not effectively cleared by host immunity. In this study, we investigate the therapeutic, antimelanoma potential of the histone deacetylase inhibitor (HDACi) panobinostat (LBH589) by assessing both its cytotoxic effects on melanoma cells as well as enhancement of immune recognition of melanoma. Utilizing murine and human melanoma cell lines, we analyzed the effects of LBH589 on proliferation and survival.

In addition, we analyzed the expression of several immunologically relevant surface markers and melanoma differentiation antigens, and the ability of LBH589-treated melanoma to activate antigen-specific T cells. Finally, we assessed the in-vivo effects of LBH589 in a mouse melanoma model. Low nanomolar concentrations of LBH589 inhibit the growth of all melanoma cell lines tested, but not normal melanocytes. This inhibition is characterized by increased apoptosis as well as a G1 cell cycle arrest. In addition, LBH589 augments the expression of major histocompatibility complex and costimulatory molecules on melanoma cells leading to an increased ability to activate antigen-specific T cells. Treatment also increases expression of melanoma differentiation antigens. In vivo, LBH589 treatment of melanoma-bearing mice results in a significant increase in survival. However, in immunodeficient mice, the therapeutic effect of LBH589 is lost. Taken together, LBH589 exerts a dual effect upon melanoma cells by affecting not only growth/survival but also by increasing melanoma immunogenicity. These effects provide the framework for future evaluation of this HDAC inhibitor in melanoma treatment.

[606]

TÍTULO / TITLE: - High cofilin-1 levels correlate with cisplatin resistance in lung adenocarcinomas.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Sep 10.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-1164-6](#)

AUTORES / AUTHORS: - Becker M; De Bastiani MA; Muller CB; Markoski MM; Castro MA; Klamt F

INSTITUCIÓN / INSTITUTION: - Laboratorio de Bioquímica Celular, Departamento de Bioquímica, ICBS/UFRGS, 2600 Ramiro Barcelos St, 90035-003, Porto Alegre, Rio Grande do Sul, Brazil.

RESUMEN / SUMMARY: - High cofilin-1 levels have been shown to be an accurate prognostic biomarker in non-small cell lung cancer (NSCLC) and a predictive factor in drug resistance. Herein we explore the role of cofilin-1 in cis-diamminedichloroplatinum(II) (cisplatin) resistance. We evaluated cofilin-1 levels in intrinsically cisplatin-resistant A549 (ICR-A549) cells and determined the cisplatin toxicity in A549 cells transiently transfected and overexpressing CFL1 plasmid. Moreover, expression levels (activity) of the CFL1 gene network were analyzed in a cisplatin-resistant human lung adenocarcinoma cell panel. ICR-A549 cells, selected by challenging parental cells with 10-fold drug GI50 value, presented a sixfold increase in cisplatin GI50 value and an increased cofilin-1 immunoccontent ($P < 0.01$). In addition, cells transfected with cofilin-1 became more resistant to cisplatin ($P < 0.01$). High activity of the CFL1 gene network was found in a cisplatin-resistant adenocarcinoma cell panel ($P < 0.01$). In vitro evidences suggest that cofilin-1 is a biological predictor of

cisplatin resistance, supporting new treatment initiatives based on cofilin-1 levels to guide chemotherapeutic interventions in NSCLC patients.

[607]

TÍTULO / TITLE: - Reduced folate carrier (RFC) as a predictive marker for response to pemetrexed in advanced non-small cell lung cancer (NSCLC).

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

REVISTA / JOURNAL: - Invest New Drugs. 2013 Aug 4.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10637-013-9992-1](#)

AUTORES / AUTHORS: - Alvarez-Fernandez C; Perez-Arnillas Q; Ruiz-Echeverria L; Rodriguez-Rubi D; Sanchez-Lorenzo L; Li-Torres W; Izquierdo-Manuel M; Berros JP; Luque-Cabal M; Jimenez-Fonseca P; Villanueva-Palicio N; Esteban-Gonzalez E

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Hospital Universitario Central de Asturias, Celestino Villamil s/n. 33006, Oviedo, Asturias, España,

carlos.alvfer@gmail.com.

RESUMEN / SUMMARY: - Introduction RFC is the major transport system in mammalian cells for folate cofactors and antifolate therapeutics. The aim of this study was to assess the predictive value of RFC expression in patients receiving pemetrexed for advanced NSCLC. Methods The study was carried out in a population of 48 patients with advanced NSCLC which have received pemetrexed monotherapy in second and third line. RFC expression was assessed using a two-step model of immunohistochemical staining in paraffin-embedded tissue samples. Results RFC expression was detected in 16 (33 %) patients. In the global population, the median progression free survival (PFS) and the median overall survival (OS) were 3.3 and 6.5 months respectively. The subgroup of patients with expression of RFC had a tendency to better median PFS (4.5 vs 2.8 months; $p = 0.926$) and median OS (11.7 vs 4.8; $p = 0.150$). In patients with adenocarcinoma histology and RFC expression median OS after treatment with pemetrexed was 14.4 months versus 5.0 in those with adenocarcinoma but without RFC expression ($p = 0.039$). Conclusions These results suggest the possible relation between RFC expression and response to treatment with antifolates (pemetrexed) independently of the tumor histology. Further studies are required to confirm these results.

[608]

TÍTULO / TITLE: - Prognostic significance of immunoglobulin M overexpression in laryngeal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Acta Otolaryngol. 2013 Oct;133(10):1080-7. doi: 10.3109/00016489.2013.799776. Epub 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [3109/00016489.2013.799776](https://doi.org/10.1007/00016489.2013.799776)

AUTORES / AUTHORS: - Wang H; Cao X; Liu EC; He D; Ma Y; Zhang T; Feng Y; Qin G

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology Head and Neck Surgery, Affiliated Hospital of Luzhou Medical College, Luzhou, P.R. China.

RESUMEN / SUMMARY: - Abstract Conclusions: Immunoglobulin (Ig) M is overexpressed in laryngeal squamous cell carcinoma (LSCC), and its expression has an independent protective impact on disease-free survival in LSCC. Objective: A number of studies have reported on the ectopic expression of Ig in cancer cells, yet there has been a lack of understanding of its clinical and prognostic significance. This study aimed to investigate the expression of IgM in resected specimens of LSCC and to evaluate its clinical significance and prognostic value. Methods: Immunohistochemistry (IHC) and Western blotting were used to detect the expression of IgM in LSCC and normal laryngeal tissues. The serum level of IgM was also analyzed by immunoturbidimetric assay. Results: IHC and Western blot studies demonstrated that IgM was overexpressed in LSCC specimens ($p < 0.001$), while the serum level of IgM in patients with LSCC was not different from healthy controls. Chi-squared analysis revealed that the expression level of IgM was negatively correlated with regional lymph node metastasis and tumor stage ($p = 0.011$ and 0.025 , respectively). Univariate analysis showed that IgM expression was significantly correlated with enhanced disease-free survival (DFS) ($p = 0.004$). In multivariate analysis, IgM retained its independent prognostic value for DFS ($p = 0.048$, HR = 0.506, 95% CI = 0.257-0.995).

[609]

TÍTULO / TITLE: - Activation of polyamine catabolic enzymes involved in diverse responses against epibrassinolide-induced apoptosis in LNCaP and DU145 prostate cancer cell lines.

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

REVISTA / JOURNAL: - Amino Acids. 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00726-013-1574-1](https://doi.org/10.1007/s00726-013-1574-1)

AUTORES / AUTHORS: - Obakan P; Arisan ED; Calcabrini A; Agostinelli E; Bolkent S; Palavan-Unsal N

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology and Genetics, Istanbul Kultur University, Atakoy Campus, Bakirkoy, 34156, Istanbul, Turkey.

RESUMEN / SUMMARY: - Epibrassinolide (EBR) is a biologically active compound of the brassinosteroids, steroid-derived plant growth regulator family. Generally, brassinosteroids are known for their cell expansion and cell division-promoting roles. Recently, EBR was shown as a potential apoptotic inducer in various cancer cells without affecting the non-tumor cell growth. Androgen signaling controls cell proliferation through the interaction with the androgen receptor (AR) in the prostate gland. Initially, the development of prostate cancer is driven by androgens. However,

in later stages, a progress to the androgen-independent stage is observed, resulting in metastatic prostate cancer. The androgen-responsive or -irresponsive cells are responsible for tumor heterogeneity, which is an obstacle to effective anti-cancer therapy. Polyamines are amine-derived organic compounds, known for their role in abnormal cell proliferation as well as during malignant transformation. Polyamine catabolism-targeting agents are being investigated against human cancers. Many chemotherapeutic agents including polyamine analogs have been demonstrated to induce polyamine catabolism that depletes polyamine levels and causes apoptosis in tumor models. In our study, we aimed to investigate the mechanism of apoptotic cell death induced by EBR, related with polyamine biosynthetic and catabolic pathways in LNCaP (AR+), DU145 (AR-) prostate cancer cell lines and PNT1a normal prostate epithelial cell line. Induction of apoptotic cell death was observed in prostate cancer cell lines after EBR treatment. In addition, EBR induced the decrease of intracellular polyamine levels, accompanied by a significant ornithine decarboxylase (ODC) down-regulation in each prostate cancer cell and also modulated ODC antizyme and antizyme inhibitor expression levels only in LNCaP cells. Catabolic enzymes SSAT and PAO expression levels were up-regulated in both cell lines; however, the specific SSAT and PAO siRNA treatments prevented the EBR-induced apoptosis only in LNCaP (AR+) cells. In a similar way, MDL 72,527, the specific PAO and SMO inhibitor, co-treatment with EBR during 24 h, reduced the formation of cleaved fragments of PARP in LNCaP (AR+) cells.

[610]

TÍTULO / TITLE: - Apoptotic pathways in ovarian surface epithelium of human embryos during embryogenesis and carcinogenesis: Close relationship of developmental plasticity and neoplasm.

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

REVISTA / JOURNAL: - Acta Histochem. 2013 Sep 19. pii: S0065-1281(13)00156-6. doi: 10.1016/j.acthis.2013.08.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.acthis.2013.08.005](#)

AUTORES / AUTHORS: - Caric A; Poljicanin A; Tomic S; Vilovic K; Saraga-Babic M; Vukojevic K

INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Histology and Embryology, School of Medicine, University of Split, Soltanska 2, Croatia.

RESUMEN / SUMMARY: - Cell differentiation and different pathways of cell death were immunohistochemically analyzed in ovaries of six human embryos, 20 serous borderline tumors (SBT) and ovarian serous carcinomas (OSC) using markers for apoptosis (caspase-3, AIF, TUNEL) and stemness (Oct-4). In the 5-8-week ovaries, caspase-3 was absent in the ovarian surface epithelium (ose) and mildly positive in the ovarian stroma (os), AIF was expressed moderately, while Oct-4 expression gradually

decreased during that period. Some ovarian cells expressed only caspase-3 or AIF together with TUNEL, while both caspase-3 and AIF were co-expressed in other ovarian cells. Mild expression of Oct-4 and caspase-3 characterized some cells of SBT, while their expression varied from mild to strong in OSC. AIF displayed mild to strong expression in ose of SBT and moderate to strong expression in OSC, while no expression of AIF was observed in os of both tumors. In the ose of both SBT and OSC, caspase-3 and AIF were co-expressed only occasionally, while AIF and Oct-4 were co-expressed strongly. Our study showed the presence of stemness cells and different pathways of cell death (caspase-3 and AIF-mediated) in the ovarian tissue during development and carcinogenesis, indicating the correlation between developmental plasticity in human embryonic ovaries and OSC.

[611]

TÍTULO / TITLE: - Baseline CD4+ T-cell counts predict HBV viral kinetics to adefovir treatment in lamivudine-resistant HBV-infected patients with or without HIV infection.

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

REVISTA / JOURNAL: - HIV Clin Trials. 2013 Jul-Aug;14(4):149-59. doi: 10.1310/hct1404-149.

●● Enlace al texto completo (gratis o de pago) [1310/hct1404-149](#)

AUTORES / AUTHORS: - Cortez KJ; Proschan MA; Barrett L; Brust DG; Weatherley B; Formentini E; Davey RT; Masur H; Polis MA; Neumann And AU; Kottlilil S

INSTITUCIÓN / INSTITUTION: - Division of Human Tissues, Office of Cell Therapy and Gene Therapies, Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville, MD, USA.

RESUMEN / SUMMARY: - BACKGROUND: Coinfection with HIV and hepatitis B virus (HBV) substantially alters the course of HBV. Directly acting anti-HBV agents suppress HBV viral levels; however, the kinetics of HBV decline in mono- and coinfecting persons have not been evaluated. We investigated the role of baseline CD4+ T-cell counts as a predictor of HBV response to adefovir (ADV) therapy in chronic HBV with and without HIV coinfection. METHODS: We conducted a double-blind, randomized, placebo-controlled study of HIV-infected (n = 12) and uninfected (n = 5) chronic HBV patients treated with ADV. Five HIV uninfected patients received ADV; the HIV+ patients received ADV or placebo for a total of 48 weeks. At the end of 48 weeks, all patients received open-label ADV for an additional 48 weeks. HBV, HIV viral loads, CD4+ T-cell counts, and safety labs were performed on days 0, 1, 3, 5, 7, 10, 14, and 28 and then every 4 weeks. RESULTS: Lower HBV slopes were observed among coinfecting compared to mono-infected patients (P = .027 at 4 weeks, P = .019 at 24 weeks, and P = .045 at 48 weeks). Using a mixed model analysis, we found a significant difference between the slopes of the 2 groups at 48 weeks (P = .045). Baseline CD4+ T-cell count was the only independent predictor of HBV decline in all patients. CONCLUSION: HIV

coinfection is associated with slower HBV response to ADV. Baseline CD4+ T-cell count and not IL28B genotype is an independent predictor of HBV decline in all patients, emphasizing the role of immune status on clearance of HBV.

[612]

TÍTULO / TITLE: - Cytotoxic, pro-apoptotic, pro-oxidant, and non-genotoxic activities of a novel copper(II) complex against human cervical cancer.

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

REVISTA / JOURNAL: - Toxicology. 2013 Sep 5. pii: S0300-483X(13)00237-0. doi: 10.1016/j.tox.2013.08.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.tox.2013.08.018](#)

AUTORES / AUTHORS: - Frias Gonzalez SE; Angeles Anguiano E; Mendoza Herrera A; Escutia-Calzada D; Ordaz Pichardo C

INSTITUCIÓN / INSTITUTION: - Laboratorio de Biología Celular y Productos Naturales, Escuela Nacional de Medicina y Homeopatía-IPN, Guillermo Massieu Helguera 239, Fracc. La Escalera, Ticoman, D.F. 07320, Mexico.

RESUMEN / SUMMARY: - Cisplatin remains one of the most effective current chemotherapeutic agents; however, metal complexes synthesis has increased in order to produce new anti-neoplastic drugs with DNA binding and apoptotic activities in tumor cells and less toxicity for patients. In this study, we evaluated the cytotoxic activity of a novel copper(II) complex (LQM402) against cervical cancer cell lines and found that LQM402 exhibited selective cytotoxicity against HeLa and Ca Ski cells. FITC-annexin assay, caspase 3/7 immunoblotting, and cytochrome c analysis, as well as a lipid peroxidation inductor activity assay based on TBARS production, indicated that the apoptotic intrinsic pathway could be involved in LQM402-induced HeLa cell death. Additionally, the Ames and micronucleus tests demonstrated non-genotoxic activity for this compound in Salmonella typhimurium and CD1 mice, respectively. Therefore, LQM402 may be a promising and safe anti-cervical cancer compound.

[613]

TÍTULO / TITLE: - Arsenic trioxide suppressed mantle cell lymphoma by downregulation of cyclin D1.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1866-2](#)

AUTORES / AUTHORS: - Lo RK; Kwong YL

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Queen Mary Hospital, University of Hong Kong, Professorial Block, Pokfulam Road, Hong Kong, China.

RESUMEN / SUMMARY: - Mantle cell lymphoma (MCL) is aggressive with poor prognosis. Due to t(11;14)(q13;q32), cyclin D1 is overexpressed. The in vitro activities of arsenic trioxide (As₂O₃) in MCL were investigated. In MCL lines Jeko-1 and Granta-519, As₂O₃ induced dose-dependent and time-dependent increases in apoptosis accompanied by cyclin D1 suppression. Downregulation of cyclin D1 resulted in decreased retinoblastoma protein phosphorylation, which led to repressed G1 progression to S/G2 phases. As₂O₃ did not affect cyclin D1 gene transcription. Instead, As₂O₃ activated glycogen synthase kinase-3beta (by tyrosine-216 phosphorylation) and IkkappaB kinase alpha/beta (by serine-176/180 phosphorylation), both of which phosphorylated cyclin D1 at threonine-286, leading to its poly-ubiquitination and degradation in the proteasome. These observations were recapitulated partly in primary MCL samples obtained from patients refractory to conventional treatment. Our findings suggested that As₂O₃ might be clinically useful in MCL.

[614]

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. 2013 Sep 20. doi: 10.4149/neo_2014_005.

●● [Enlace al texto completo \(gratis o de pago\) 4149/neo_2014_005](#)

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.

[615]

TÍTULO / TITLE: - Apoptosis of Human Gastric Carcinoma SGC-7901 Induced by Deoxycholic Acid via the Mitochondrial-Dependent Pathway.

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

REVISTA / JOURNAL: - Appl Biochem Biotechnol. 2013 Oct;171(4):1061-71. doi: 10.1007/s12010-013-0417-6. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1007/s12010-013-0417-6](#)

AUTORES / AUTHORS: - Song W; Yang HB; Chen P; Wang SM; Zhao LP; Xu WH; Fan HF; Gu X; Chen LY

INSTITUCIÓN / INSTITUTION: - School of Life Sciences and Engineering, Henan University of Urban Construction, Pingdingshan, 467044, Henan, China.

RESUMEN / SUMMARY: - The study aimed to evaluate the effects of deoxycholic acid (DCA) on human gastric carcinoma cell lines and to explore its mechanisms. In the present study, effects of DCA on SGC-7901 cell growth, cell cycle, and apoptosis were investigated by MTT assay, inverted microscopy, fluorescence microscopy, PI single- and FITC/PI double-staining flow cytometry, and western blotting. The study have revealed that DCA significantly inhibited the growth of SGC-7901 cells in a dose- and time-dependent manner and arrested cell cycle at G0/G1 phase. SGC-7901 cells showed typical apoptotic morphological changes after treated with DCA for 48 h. The intensity of typical apoptosis pattern- "ladders" formed by DNA in fragments of multiples of 200 base pairs was also observed. Apoptosis of SGC-7901 cells induced by DCA were associated with collapse of the mitochondrial membrane potential. DCA treatment could also increase the ratio of Bax to Bcl-2 in SGC-7901 cells. Meanwhile, the expression of p53, cyclinD1, and c-Myc were changed after DCA treatment. These results suggest that DCA induces apoptosis of gastric carcinoma cells through an intrinsic mitochondrial-dependent pathway, and the increase in the Bax/Bcl-2 ratio and collapse of the mitochondrial membrane potential may play important roles in DCA-induced apoptosis of gastric carcinoma cells.

[616]

TÍTULO / TITLE: - Renal Carcinoma Cell-Derived Exosomes Induce Human Immortalized Line of Jurkat T Lymphocyte Apoptosis in vitro.

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

REVISTA / JOURNAL: - Urol Int. 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1159/000348747](#)

AUTORES / AUTHORS: - Yang L; Wu X; Wang D; Luo C; Chen L

INSTITUCIÓN / INSTITUTION: - Department of Urology, The First Affiliated Hospital, Chongqing Medical University, Chongqing, PR China.

RESUMEN / SUMMARY: - Objective: Tumor-derived exosomes usually contain some molecules that can help immune evasion by tumors. This study is aimed at investigating the potential effect of exosomes from human kidney adenocarcinoma cells on a human immortalized line of Jurkat T lymphocytes in vitro. Methods: Exosomes were purified from human kidney adenocarcinoma ACHN cells by sequential

centrifugations and ultrafiltrations, and characterized by transmission electron microscopy. The effects of exosomes on the proliferation, cytokine production and apoptosis of Jurkat T cells were determined using flow cytometry and enzyme-linked immunosorbent assay. The relative levels of pro- and anti-apoptotic molecules were determined by Western blotting. Results: Exosomes were purified from ACHN cells and exhibited typical characteristics. Treatment with exosomes inhibited Jurkat T cell proliferation and induced Jurkat T cell apoptosis in a dose- and time-dependent manner. Treatment with exosomes reduced spontaneous interleukin-2 (IL-2), interferon-gamma, IL-6 and IL-10 production by Jurkat T cells. Treatment with exosomes increased the relative levels of cleaved caspase-3, -8 and -9 as well as Bax, but reduced the levels of Bcl-2 in Jurkat T cells. The purified exosomes contained Fas ligand, and treatment with soluble Fas abrogated exosome-mediated Jurkat T cell apoptosis. Conclusions: Our data indicate that exosomes from kidney adenocarcinoma cells contain Fas ligand and trigger Jurkat T cell apoptosis, contributing to the immune evasion of tumors.

[617]

TÍTULO / TITLE: - Different susceptibility of colon cancer DLD-1 and LOVO cell lines to apoptosis induced by DMU-212, a synthetic resveratrol analogue.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Sep 19. pii: S0887-2333(13)00221-X. doi: 10.1016/j.tiv.2013.09.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.09.012](#)

AUTORES / AUTHORS: - Piotrowska H; Myszkowski K; Amarowicz R; Murias M; Kulcenty K; Wierzchowski M; Jodynis-Liebert J

INSTITUCIÓN / INSTITUTION: - Department of Toxicology, Poznan University of Medical Sciences, Poznan, Poland. Electronic address: hanna.piotrowska@ump.edu.pl.

RESUMEN / SUMMARY: - The cytotoxic activity of DMU-212 has been shown to vary in cell lines derived from the same type of cancer, i.e. ovarian, breast and colorectal ones. However, the molecular mechanism of DMU-212 cytotoxicity has not been clarified in colon cancer cells. This study aims to elucidate the mechanism of antitumor effects of DMU-212 in two human colon cancer cell lines, DLD-1 and LOVO. We showed the stronger cytotoxic activity in DLD-1 cells in which DMU-212 evoked a greater pro-apoptotic effect as compared to that of LOVO cells. The analysis of the expression pattern of 84 apoptosis-related genes indicated transcripts specific to the mitochondria-mediated apoptosis pathway in both colon cancer cell lines used. We found that DMU-212 caused up-regulation of pro-apoptotic Bak1, Bok, Bik, Noxa, Bad, Bax, p53 and Apaf1 transcripts level in DLD-1 cell line, whereas anti-apoptotic Bcl-2, Bcl-xL and Bag1 mRNA expression was decreased. Changes in apoptosis-related genes expression were less pronounced in LOVO cells which did not express CYP1B1 protein

and showed lower expression of CYP1A1 protein level than that in DLD-1 cells. Our results suggest that anticancer activity of DMU-212 is closely related to its biotransformation catalysed by these cytochrome P450 isoenzymes.

[618]

TÍTULO / TITLE: - Efficacy of liposomal curcumin in a human pancreatic tumor xenograft model: inhibition of tumor growth and angiogenesis.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Sep;33(9):3603-9.

AUTORES / AUTHORS: - Ranjan AP; Mukerjee A; Helson L; Gupta R; Vishwanatha JK

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology and Immunology, and Institute for Cancer Research, Graduate School of Biomedical Sciences, University of North Texas Health Science Center, Fort Worth, Texas, 76107, USA.

Jamboor.vishwanatha@unthsc.edu.

RESUMEN / SUMMARY: - BACKGROUND: Liposome-based drug delivery has been successful in the past decade, with some formulations being Food and Drug Administration (FDA)-approved and others in clinical trials around the world. The major disadvantage associated with curcumin, a potent anticancer agent, is its poor aqueous solubility and hence low systemic bioavailability. However, curcumin can be encapsulated into liposomes to improve systemic bioavailability. MATERIALS AND METHODS: We determined the antitumor effects of a liposomal curcumin formulation against human MiaPaCa pancreatic cancer cells both in vitro and in xenograft studies. Histological sections were isolated from murine xenografts and immunohistochemistry was performed. RESULTS: The in vitro (IC50) liposomal curcumin proliferation-inhibiting concentration was 17.5 µM. In xenograft tumors in nude mice, liposomal curcumin at 20 mg/kg i.p. three-times a week for four weeks induced 42% suppression of tumor growth compared to untreated controls. A potent antiangiogenic effect characterized by a reduced number of blood vessels and reduced expression of vascular endothelial growth factor and annexin A2 proteins, as determined by immunohistochemistry was observed in treated tumors. CONCLUSION: These data clearly establish the efficacy of liposomal curcumin in reducing human pancreatic cancer growth in the examined model. The therapeutic curcumin-based effects, with no limiting side-effects, suggest that liposomal curcumin may be beneficial in patients with pancreatic cancer.

[619]

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

REVISTA / JOURNAL: - J Hum Hypertens. 2013 Sep 26. doi: 10.1038/jhh.2013.91.

●● Enlace al texto completo (gratis o de pago) [1038/jhh.2013.91](#)

AUTORES / AUTHORS: - Rubin S; Lacraz A; Galantine V; Gosse P

INSTITUCIÓN / INSTITUTION: - Renal Unit, Hopital de la Cote Basque, Bayonne, France.

[620]

TÍTULO / TITLE: - Proteasome inhibition leads to altered signaling in the proteome of cisplatin-resistant human ovarian carcinoma cell line.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(6):627-34. doi: 10.4149/neo_2013_081.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2013_081](#)

AUTORES / AUTHORS: - Duraj J; Pastorek M; Vitkovska J; Cholujoval D; Gronosova P; Hunakova L; Sedlak J

RESUMEN / SUMMARY: - To address precise view into molecular mechanisms of apoptotic signaling pathways after single- or combinatory treatments with specific NF-kappaB- or proteasome inhibitors and/or cisplatin (CDDP), flow cytometry and western blotting of the cell proteome in human ovarian chemosensitive- and CDDP-resistant cell lines were used. We report here that proteasome inhibition (but not NF-kappaB inhibition) caused marked alterations in the cell proliferation and cell cycle, as well as in the levels of signaling anti- and pro-apoptotic proteins PARP, NF-kappaB, I kappa B-alpha, Bcl-2, Bax, and lysosome-associated LAMP-1 and ATP-7B molecules in particular proteome fractions. These findings refer to the possibility of regulation of CDDP resistance, inclusive the capacity of lysosomes to export CDDP in certain human ovarian cancer cells by proteasome inhibition. Keywords: cisplatin resistance, cell proteome, NF-kappaB- and proteasome inhibition, flow cytometry, western blotting.

[621]

TÍTULO / TITLE: - Identification of intermediate risk breast cancer patients with 1-3 positive lymph nodes and excellent survival after tamoxifen as only systemic adjuvant therapy by use of markers of proliferation and apoptosis.

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

REVISTA / JOURNAL: - Breast. 2013 Oct;22(5):643-9. doi: 10.1016/j.breast.2013.07.043. Epub 2013 Aug 19.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.07.043](#)

AUTORES / AUTHORS: - Linderholm BK; Linder S; Arnesson LG; Stal O

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Sahlgrenska Academy and University Hospital, Gothenburg, Sweden; Department of Oncology/Pathology, Karolinska Institutet, Stockholm, Sweden. Electronic address: barbro.linderholm@ki.se.

RESUMEN / SUMMARY: - BACKGROUND: According to current guidelines, patients with primary breast cancer and 1-3 lymph node metastases will in general be offered adjuvant chemotherapy. AIM: Our objective was to investigate the relationship

between markers of proliferation and apoptosis with survival for patients subjected to adjuvant tamoxifen solely. MATERIAL AND METHODS: Tumour cytosol samples from 409 consecutive patients with operable oestrogen receptor positive BC, stage I-III and treated with tamoxifen for 2 or 5 years were assessed for levels of caspase-cleaved cytokeratin-18 (ccCK18), an indicator of apoptosis, by use of an ELISA assay. Data on S-phase fraction (SPF) were available for 370 patients. Survival analyses were performed according to levels of ccCK18 and SPF separately, as well as combined. RESULTS: A wide range of ccCK18 protein levels was found, median 9.97, range 0.0-87.3 pg/mugDNA. Increasing SPFs were significantly associated with a lower distant recurrence-free survival (DRFS) ($p = 0.025$) and breast cancer survival (BCS) ($p = 0.046$). In the group with low SPF (below mean), low amounts of ccCK18 correlated with a shorter DRFS ($p = 0.0028$) and BCS ($p = 0.0027$). A Proliferation Index (PI); a quotient of ccCK18/SPF was constructed. Low PI (high ccCK18/SPF ratios) were significantly correlated with an improved survival both when analysed as continuous variables; DRFS ($p = 0.021$), BCS ($p = 0.038$) and when divided into quartiles; DRFS ($p < 0.001$) and BCS ($p = 0.0012$). A similar correlation was found in patients with 1-3 lymph node metastases; DRFS ($p = 0.089$) and BCS ($p = 0.019$). A Cox's proportional hazard model including age, tumour size, lymph node status, PgR and ccCK18/SPF was used for multivariate analysis. High ccCK18/SPF ratios correlated with improved survival; DRFS (HR = 0.47 (0.22-0.98), $p = 0.043$), and BCS (HR = 0.39 (0.16-1.00), $p = 0.049$), respectively. CONCLUSION: By use of a proliferation index based on markers of proliferation and apoptosis, a group of patients with 1-3 lymph node metastases with good outcome following adjuvant tamoxifen was identified; this group could possibly be spared adjuvant chemotherapy.

[622]

TÍTULO / TITLE: - Vascular endothelial growth factor polymorphisms and clinical outcome in patients with metastatic breast cancer treated with weekly docetaxel.

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

REVISTA / JOURNAL: - Pharmacogenomics J. 2013 Sep 24. doi: 10.1038/tpj.2013.36.

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

AUTORES / AUTHORS: - Koutras AK; Kotoula V; Papadimitriou C; Dionysopoulos D; Zagouri F; Kalofonos HP; Kourea HP; Skarlos DV; Samantas E; Papadopoulou K; Kosmidis P; Pectasides D; Fountzilas G

INSTITUCIÓN / INSTITUTION: - Division of Oncology, Department of Medicine, University Hospital, University of Patras Medical School, Patras, Greece.

RESUMEN / SUMMARY: - The aim of the study was to evaluate the association of vascular endothelial growth factor (VEGF) genotypes with treatment efficacy in a phase II trial. This study evaluated weekly docetaxel, as first-line treatment for metastatic breast cancer. Existing data from in vitro and animal model experiments suggest that

docetaxel at low doses has anti-angiogenic activity. DNA was extracted from blood samples of 86 patients participating in the trial. Genotyping was performed for selected single-nucleotide polymorphisms (SNPs; VEGF-2578, -1498, -1154, and +936). Moreover, due to the highly polymorphic nature of the studied areas, we were able to analyze additional registered SNPs. All candidate genotypes were evaluated for associations with overall survival (OS), progression-free survival (PFS) and response rate. The VEGF-1154 GG genotype was more frequent in patients not responding to treatment compared with responders (42.9% vs 0.0%, $P=0.048$). Moreover, the VEGF-2578 AA genotype was associated with longer PFS compared with CC (hazard ratio (HR)=0.40; 95% confidence interval (CI) 0.17-0.98; pairwise $P=0.0457$). Patients with the VEGF-1190 GG genotype demonstrated shorter PFS compared with those with the alternative genotypes (GA and AA) combined (HR=3.85; 95% CI: 1.20-12.50; $P=0.0224$). In addition, the VEGF-2551/-2534 homozygous del18bp and VEGF-2430/-2425 homozygous ins1bp genotypes were associated with worse PFS compared with no deletion and no insertion, respectively (HR=2.49; 95% CI: 1.02-6.07; pairwise $P=0.0442$ and HR=2.57; 95% CI: 1.05-6.27; pairwise $P=0.0385$, respectively). Furthermore, patients with the VEGF-1498 CC genotype exhibited longer median OS compared with those with the alternatives genotypes (CT and TT) combined (HR=0.27; 95% CI: 0.08-0.89; $P=0.0311$). In multivariate analysis, the VEGF-2578 AA genotype retained its significance ($P=0.0220$) for PFS. Our results support the association of specific VEGF genotypes with clinical outcome in patients with metastatic breast cancer treated with a potentially anti-angiogenic regimen, such as weekly docetaxel. However, current results should be validated prospectively in larger cohorts. *The Pharmacogenomics Journal* advance online publication, 24 September 2013; doi:10.1038/tpj.2013.36.

[623]

TÍTULO / TITLE: - Reaction of plasma adiponectin level in non-small cell lung cancer patients treated with EGFR-TKIs.

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

REVISTA / JOURNAL: - Osaka City Med J. 2013 Jun;59(1):53-60.

AUTORES / AUTHORS: - Umekawa K; Kimura T; Kudoh S; Suzumura T; Nagata M; Mitsuoka S; Matsuura K; Oka T; Yoshimura N; Kira Y; Hirata K

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Osaka City University, Graduate School of Medicine, Japan. m2043009@med.osaka-cu.ac.jp

RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are routinely used to treat advanced non-small cell lung cancer (NSCLC) patients with activated EGFR mutations, and are associated with excellent response and improvement of performance status. Adipose tissue produces and releases substances called adipokines, which include adiponectin, leptin, resistin, and hepatocyte growth factor (HGF), etc. Previously, we reported that high levels of

plasma HGF at diagnosis indicated intrinsic resistance to EGFR-TKIs. EGFR-TKIs have been hypothesized to affect these adipokines. METHODS: This prospective study, to evaluate the correlation between plasma adiponectin and insulin levels and non-hematological adverse effects in advanced NSCLC following EGFR-TKIs administration, was conducted at the Osaka City University Hospital. Plasma adiponectin and insulin levels were determined at diagnosis and on treatment day 30. RESULTS: Overall 33 patients were enrolled. We obtained plasma samples for analyses from all patients at diagnosis and from 26 patients on day 30. Increased adiponectin (13.69 to 14.42 microg/mL, $p = 0.0092$), and decreased insulin (404.0 to 351.2 pg/mL, $p = 0.022$) were observed after EGFR-TKI treatments. High levels of adiponectin at diagnosis were associated with severities of skin rash ($p = 0.035$). CONCLUSIONS: The adiponectin was affected by EGFR-TKI treatments for NSCLC. Besides, the adverse events by EGFR-TKIs were influenced by the plasma adipokines at diagnosis. Our study may provide useful information regarding patient outcomes to EGFR-TKI treatments. A prospective large clinical trial is warranted to clarify these results.

[624]

TÍTULO / TITLE: - Prognostic Value of the Combination of Circulating Tumor Cells Plus KRAS in Patients With Metastatic Colorectal Cancer Treated With Chemotherapy Plus Bevacizumab.

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

REVISTA / JOURNAL: - Clin Colorectal Cancer. 2013 Sep 5. pii: S1533-0028(13)00070-4. doi: 10.1016/j.clcc.2013.06.001.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clcc.2013.06.001](#)

AUTORES / AUTHORS: - Sastre J; Vidaurreta M; Gomez A; Rivera F; Massuti B; Lopez MR; Abad A; Gallen M; Benavides M; Aranda E; Rubio ED

INSTITUCIÓN / INSTITUTION: - Medical Oncology Department, HC San Carlos, Madrid, España (Center affiliated with the Red Tematica de Investigacion Cooperativa (RD06/0020/0021), Instituto Carlos III, Spanish Ministry of Science and Innovation, Madrid, España). Electronic address: jsastre.hcsc@salud.madrid.org.

RESUMEN / SUMMARY: - OBJECTIVE: Circulating tumor cells (CTCs) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) status were identified as prognostic factors for progression-free survival (PFS) and overall survival (OS) in patients with metastatic colorectal cancer treated with chemotherapy and bevacizumab in analyses of the MACRO (Maintenance Treatment in Advanced Colorectal Cancer) trial. In this post hoc analysis of the MACRO trial, the potential additive effect of these 2 factors on patient outcomes was explored. METHODS: A total of 158 of the 480 patients involved in the MACRO trial were included in the biological marker substudy. CTC isolation and enumeration were centralized and performed using the CellSearch System (Veridex LLC, Raritan, NJ) in 7.5 mL of whole blood. Evaluation of KRAS status was performed

retrospectively by the standard method used at each center. PFS and OS were analyzed by the Kaplan-Meier method according to CTC count and KRAS status. RESULTS: Patients with < 3 CTC per 7.5 mL blood at baseline and KRAS wild-type tumors had a median PFS of 14.2 months compared with 6.2 months in patients with \geq 3 CTCs and KRAS mutated tumors ($P < .0001$; hazard ratio, 3.0; 95% confidence interval, 1.8-5.2). Similar findings were observed for OS (28.9 and 13.7 months, respectively, $P = .0004$; hazard ratio 2.8; 95% confidence interval, 1.6-4.9). Multivariate analyses showed that CTC count \geq 3 and KRAS status were the only independent prognostic factors for both PFS and OS. CONCLUSIONS: This post hoc analysis showed that CTC count and KRAS status were independent prognostic factors for outcomes in patients with metastatic colorectal cancer treated with bevacizumab +/- chemotherapy. These factors should be taken into account in the design of future phase III trials.

[625]

TÍTULO / TITLE: - Triptolide induces apoptosis and inhibits the growth and angiogenesis of human pancreatic cancer cells by downregulating COX-2 and VEGF.

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

REVISTA / JOURNAL: - Oncol Res. 2013;20(8):359-68. doi: 10.3727/096504013X13657689382932.

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

[3727/096504013X13657689382932](#)

AUTORES / AUTHORS: - Ma JX; Sun YL; Wang YQ; Wu HY; Jin J; Yu XF

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - Triptolide (TPL) inhibits the growth and proliferation of a wide range of human cancer cells, but the underlying mechanism is largely unknown. Here, we report that TPL induces apoptosis and inhibits proliferation of PANC-1 pancreatic cancer cells by downregulating cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF). Cell viability and apoptosis were measured by MTT assay and flow cytometry. Real-time PCR and Western blot were used to examine the expression of COX-2 and VEGF. The Matrigel angiogenesis and Transwell migration were employed to assess tube formation and cell migration. Pancreatic cancer mouse xenografts were established to investigate the in vivo antitumor effects of TPL. TUNEL staining and immunohistochemistry were used to detect the apoptosis rate and protein expression in tumor tissues. TPL inhibited the proliferation of pancreatic cancer cells in a time and concentration-dependent manner and decreased the expression of COX-2 and VEGF in vitro. Furthermore, medium from TPL-treated PANC-1 cells inhibited the proliferation, migration, and tube formation of HUVECs. TPL significantly reduced the growth of pancreatic cancer mouse xenografts, accompanied

by an induction of apoptosis, inhibition of angiogenesis, and reduction of COX-2 and VEGF. Our data indicate that suppressing the expression of COX-2 and VEGF may be one of the molecular mechanisms by which TPL induces apoptosis and inhibits the growth and angiogenesis of human pancreatic cancer cells.

[626]

TÍTULO / TITLE: - Is Minimal Residual Lymph Node Disease in Papillary Thyroid Cancer of Prognostic Impact? An Analysis of The Epithelial Cell Adhesion Molecule EpCAM in Lymph Nodes of 40 pN0 Patients.

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

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Aug 6.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12253-013-9682-5](#)

AUTORES / AUTHORS: - Rehders A; Anlauf M; Adamowsky I; Ghadimi MH; Klein S; Antke C; Cupisti K; Stoecklein NH; Knoefel WT

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Heinrich Heine University, Dusseldorf, Germany, rehders@med.uni-duesseldorf.de.

RESUMEN / SUMMARY: - This study was aimed to assess the extend of nodal microdissemination in patients with pN0 papillary thyroid carcinoma (PTC) using immunohistochemical analysis. In early stage PTC both, systematic lymphadenectomy as well as radio iodine treatment, aimed to eliminate occult nodal tumor involvement, are under controversial debate, since little is known about the extend of lymphatic microdissemination in these patients. Formalin embedded samples of the resected lymph nodes were systematically screened for the presence of disseminated tumor cells using immunohistochemistry (monoclonal antibody Ber-EP4). Clinical and histopathological parameters as well as the post-operative course were recorded. Survival data were analysed by the Kaplan-Meier method and the log rank test. Overall 321 lymph nodes of 40 patients were screened immunohistochemically. In 12.5 % of the patients disseminated occult tumor cells were diagnosed. In addition to tumor resection 90 % of the patients underwent adjuvant radio-iodine treatment. The mean observation period in our collective was 72 months. The detection of disseminated tumor cells did not correlate with clinicopathologic risk parameters and did not have significant influence on the prognosis of these patients. Immunohistochemical analysis enables the detection of disseminated tumor cells in patients with pN0 PTC. This finding seems to support the application of adjuvant radio iodine, even in early tumor stages.

[627]

TÍTULO / TITLE: - Trastuzumab Retreatment after Relapse on Adjuvant Trastuzumab Therapy for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Final Results of the Retreatment after Herceptin Adjuvant Trial.

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

REVISTA / JOURNAL: - Clin Oncol (R Coll Radiol). 2013 Sep 16. pii: S0936-6555(13)00329-4. doi: 10.1016/j.clon.2013.08.011.

●● Enlace al texto completo (gratis o de pago) 1016/j.clon.2013.08.011

AUTORES / AUTHORS: - Lang I; Bell R; Feng FY; Lopez RI; Jassem J; Semiglazov V; Al-Sakaff N; Heinzmann D; Chang J

INSTITUCIÓN / INSTITUTION: - National Institute of Oncology, Budapest, Hungary.

Electronic address: lang@oncol.hu.

RESUMEN / SUMMARY: - AIMS: Trastuzumab, in combination with chemotherapy, is the standard of care for patients with early and metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The Retreatment after HERceptin Adjuvant trial assessed the efficacy and safety of trastuzumab plus a taxane as first-line treatment for patients with metastatic breast cancer (MBC) who had relapsed after adjuvant trastuzumab for HER2-positive early breast cancer. MATERIALS AND METHODS: In total, 43 patients with HER2-positive MBC who had received previous adjuvant trastuzumab for ≥ 10 months, with a relapse-free interval of ≥ 6 months after the last adjuvant trastuzumab dose, were recruited. Eligible patients ($n = 41$) were assigned to receive trastuzumab, either weekly or every 3 weeks, in combination with docetaxel or paclitaxel until disease progression. RESULTS: At the final analysis, with a median follow-up time of 40 months, a positive response was observed in 25/41 patients (61%; 95% confidence interval: 48.7-80.4%), stable disease in 7/41 (17.1%) and progressive disease in 6/41 (14.6%). Three patients had missing response assessments (one had no measurable lesions at baseline and two had no post-baseline tumour assessments). The median progression-free survival (PFS) was 8.0 months (95% confidence interval: 6-11 months) and the median overall survival was 25.0 months (16-33 months). No correlation was found between response rate, PFS or overall survival and the duration of adjuvant trastuzumab treatment, trastuzumab-free interval, relapse-free interval, hormone receptor status or type of pre-metastatic treatment. The most common adverse events (all grades) were alopecia (32%) and diarrhoea (32%). Six patients (14.6%) developed at least one serious adverse event. No congestive heart failure or any unexpected adverse events were reported. CONCLUSION: Trastuzumab, in combination with a taxane, is an effective and well-tolerated first-line treatment for MBC in patients who relapse after trastuzumab-based adjuvant therapy.

TÍTULO / TITLE: - Intergenic polymorphisms in the amphiregulin gene region as biomarkers in metastatic colorectal cancer patients treated with anti-EGFR plus irinotecan.

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

REVISTA / JOURNAL: - Pharmacogenomics J. 2013 Aug 20. doi: 10.1038/tpj.2013.29.

●● Enlace al texto completo (gratis o de pago) [1038/tpj.2013.29](#)

AUTORES / AUTHORS: - Sebio A; Paez D; Salazar J; Berenguer-Llargo A; Pare-Brunet L; Lasa A; Del Rio E; Tobena M; Martin-Richard M; Baiget M; Barnadas A

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Santa Creu i Sant Pau Hospital, Autònoma University of Barcelona, Barcelona, España.

RESUMEN / SUMMARY: - In the epidermal growth factor receptor (EGFR) pathway, polymorphisms in EGFR and its ligand EGF have been studied as biomarkers for anti-EGFR treatment. However, the potential pharmacogenetic role of other EGFR ligands such as amphiregulin (AREG) and epiregulin (EREG) has not been elucidated. We studied 74 KRAS and BRAF wild-type metastatic colorectal cancer patients treated with anti-EGFR plus irinotecan. Twenty-two genetic variants in EGFR, EGF, AREG and EREG genes were selected using HapMap database and literature resources. Three tagging single-nucleotide polymorphisms in the AREG gene region (rs11942466 C>A, rs13104811 A>G, and rs9996584 C>T) predicted disease control in the multivariate analyses. AREG rs11942466 C>A and rs9996584 C>T were also associated with overall survival (OS). The functional polymorphism, EGFR rs712829 G>T, was associated with progression-free and OS. Our findings support that intergenic polymorphisms in the AREG gene region might help to identify colorectal cancer patients that will benefit from irinotecan plus anti-EGFR therapy. The Pharmacogenomics Journal advance online publication, 20 August 2013; doi:10.1038/tpj.2013.29.

[629]

TÍTULO / TITLE: - Treatment of Chronic Myeloid Leukemia Elderly Patients in the Tyrosine Kinase Inhibitor Era.

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

REVISTA / JOURNAL: - Curr Cancer Drug Targets. 2013 Sep;13(7):755-767.

AUTORES / AUTHORS: - Russo D; Malagola M; Skert C; Fili C; Bergonzi C; Cancelli V; Cattina F

INSTITUCIÓN / INSTITUTION: - Chair of Hematology, Unit of Blood Diseases and Cell Therapies, University of Brescia - AO Spedali Civili Brescia, P.le Spedali Civili 1, 25100 Brescia, Italy. russo@med.unibs.it.

RESUMEN / SUMMARY: - The prevalence of chronic myeloid leukemia (CML) is expected to double in the next 15 years. The introduction of imatinib significantly changed the prognosis of CML, challenging the concept of a fatal disease. Nowadays, imatinib, nilotinib and dasatinib are registered for first-line treatment of CML patients in

chronic phase (CP). Considering elderly patients, the most extensively studied TKI is imatinib, that induces a rate of cytogenetic and molecular responses comparable between the younger and the elderly patients. Once a CCgR with imatinib is achieved, the probability to be alive and disease free at 8 years is more than 80%. These results confirm that imatinib has to be considered the first-line treatment for the elderly and that the CCgR is the guide parameter for treatment modulation and the most solid marker of long term outcome. Nevertheless, older patients tolerate imatinib worse in comparison to the younger, and this causes a higher rate of therapy discontinuation and less adherence to chronic treatment. Thus, the toxic profile of each TKI is one of the most important factors driving the choice of the best drug. Another important factor is the potency of the TKI. Since nilotinib and dasatinib are more potent than imatinib in inducing cytogenetic and molecular responses, they could be preferred for increasing the proportion of patients who can achieve deeper molecular responses, allowing treatment discontinuation. This approach is intriguing, but it is still experimental. Another therapeutic strategy could be the identification of the minimal effective dose of TKI in order to maintain the CCgR, but also this approach is under clinical investigation.

[630]

TÍTULO / TITLE: - Clinical significance of plasma fibrinogen level as a predictive marker for postoperative recurrence of esophageal squamous cell carcinoma in patients receiving neoadjuvant treatment.

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

REVISTA / JOURNAL: - Dis Esophagus. 2013 Aug 27. doi: 10.1111/dote.12115.

●● [Enlace al texto completo \(gratis o de pago\) 1111/dote.12115](#)

AUTORES / AUTHORS: - Matsuda S; Takeuchi H; Fukuda K; Nakamura R; Takahashi T; Wada N; Kawakubo H; Saikawa Y; Omori T; Kitagawa Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Keio University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - Among multidisciplinary therapies developed for advanced esophageal cancer, neoadjuvant chemotherapy and chemoradiotherapy have been established as standard treatments. To deliver cautious follow up and intense treatment for high-risk patients, a simple and instructive biomarker for the postoperative recurrence needs to be identified. Fibrinogen, a common component of hemostasis, has been suggested to not only play an important role in cancer metastasis, but also correlate with tumor recurrence. We aim to clarify the validity of plasma fibrinogen as a marker for predicting the postoperative recurrence of esophageal squamous cell carcinoma patients who received neoadjuvant treatment. We reviewed 72 consecutive patients with esophageal squamous cell carcinoma who received neoadjuvant chemotherapy or chemoradiotherapy, followed by

esophagectomy at the Keio University Hospital from 2001 to 2010. Of them, we retrospectively examined 68 patients who underwent plasma fibrinogen examination before and after neoadjuvant treatment and underwent transthoracic radical esophagectomy. We investigated patient characteristics, clinicopathological factors, neoadjuvant treatment effects, postoperative course, and plasma fibrinogen levels. We investigated pretreatment and preoperative (postneoadjuvant treatment) plasma fibrinogen levels, as well as changes in fibrinogen levels before and after neoadjuvant treatment. Patients with preoperative hyperfibrinogenemia (>350 mg/dL) and patients with increased plasma fibrinogen levels during neoadjuvant treatment showed significantly shorter postoperative disease-free survival (DFS) (P = 0.002 and P = 0.037, respectively). Moreover, we classified these patients into three classes on the basis of their preoperative fibrinogen levels and changes in fibrinogen levels during neoadjuvant treatment. Patients who had both high preoperative plasma fibrinogen and increased fibrinogen levels showed significantly shorter DFS than others. In contrast, patients who had normal preoperative plasma fibrinogen and decreased fibrinogen levels showed significantly longer DFS. Based on this fibrinogen classification, we could differentiate between significantly favorable and poor prognosis patients group. Overall, this classification (hazard ratio = 1.812, P = 0.013) and the response to neoadjuvant treatment (hazard ratio = 0.350, P = 0.007) were found to be significant determining factors for postoperative DFS. With the validity of preoperative plasma fibrinogen levels and changes in fibrinogen levels during neoadjuvant treatment, the plasma fibrinogen level was found to be a possible biomarker for postoperative recurrence in advanced esophageal cancer patients who received neoadjuvant treatment. Moreover, plasma fibrinogen classification could be a simple and valuable predictive marker for postoperative follow up.

[631]

TÍTULO / TITLE: - Oldhamianoside II, a new triterpenoid saponin, prevents tumor growth via inducing cell apoptosis and inhibiting angiogenesis.

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

REVISTA / JOURNAL: - Oncol Res. 2013;20(8):369-76. doi: 10.3727/096504013X13657689382978.

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

[3727/096504013X13657689382978](#)

AUTORES / AUTHORS: - Wang FL; Sun JY; Wang Y; Mu YL; Liang YJ; Chong ZZ; Qin SH; Yao QQ

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Shandong Academy of Medical Sciences, Jinan, China.

RESUMEN / SUMMARY: - Oldhamianoside II is a new triterpenoid saponin that was isolated from the roots of *Gypsophila oldhamiana*. The present study aims to

investigate the potential inhibitory activity of oldhamianoside II on tumor growth using an S180 tumor implantation mouse model. Oldhamianoside II at doses of 5.0 and 10.0 mg/kg was given with intraperitoneal injection for 10 days following subcutaneous inoculation of S180 tumor cells in anterior flank of mice. The tumor growth, the cell apoptosis, the microvessel density (MVD) in S180 tumors, the tumor cell viability, the tubular formation in vitro, and migration of tumor cells were examined. The expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and cyclooxygenase-2 (COX-2) was determined to analyze the associated mechanisms. The results showed that oldhamianoside II potently inhibited tumor cell viability in vitro. In addition, oldhamianoside II delayed tumor growth in anterior flank, induced S180 cell apoptosis, and reduced the MVD. Oldhamianoside II was also demonstrated to decrease the number of tubular structure and vessel formation in HUVEC cultures and chick embryo chorioallantoic membrane (CAM) model, respectively. Further study indicated that oldhamianoside II reduced the expression of VEGF, bFGF, and COX-2 in tumor sections. Moreover, oldhamianoside II inhibited the activity of migration and penetration to Matrigel of SGC7901 tumor cells in scratch wound and transwell chamber. In conclusion, our work defines oldhamianoside II, a new triterpenoid saponin, as a novel compound that can effectively inhibit S180 tumor growth, induce tumor cell apoptosis, prevent tumor angiogenesis, and inhibit cancer cell migration, suggesting that oldhamianoside II is a potential drug candidate for the treatment of cancer and for the prevention of metastasis.

[632]

TÍTULO / TITLE: - Single agent panitumumab in KRAS wild-type metastatic colorectal cancer patients following cetuximab-based regimens: Clinical outcome and biomarkers of efficacy.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Sep 4;14(12).

AUTORES / AUTHORS: - Pietrantonio F; Perrone F; Biondani P; Maggi C; Lampis A; Bertan C; Venturini F; Tondulli L; Ferrari D; Ricci V; Villa F; Barone G; Bianco N; Ghidini A; Bossi I; Fanetti G; Di Bartolomeo M; de Braud F

INSTITUCIÓN / INSTITUTION: - Medical Oncology Department; Fondazione I.R.C.C.S. Istituto Nazionale Tumori; Milan, Italy.

RESUMEN / SUMMARY: - Background Few data are available outlining outcomes of panitumumab in advanced colorectal cancer patients benefiting from prior cetuximab-based regimens. Patients and Methods Thirty patients with KRAS wild type metastatic colorectal cancer with clinical benefit from prior cetuximab-based regimens between May 2004 and October 2011 were reviewed at nine Italian Institutions. Inclusion key criteria included interruption of cetuximab for reasons other than progressive disease. Patients were classified according to prior regimens (0 or ≥ 1), prior response or

stabilization, surgery of metastases, and Kohne prognostic score. At the time of subsequent progression, patients were treated with single agent panitumumab until progressive disease, unacceptable toxicity or consent withdrawal. Results Panitumumab obtained 67% disease control rate and 30% objective response rate, with median PFS of 4.2 and median OS of 9.6 mo. Patients with BRAF/NRAS/PI3KCA and KRAS (by mutant enriched technique) wild-type tumors had the best chance of response to panitumumab. Conclusions Single agent panitumumab provided significant clinical benefit in heavily pretreated patients without acquired resistance to prior cetuximab-based regimens.

[633]

TÍTULO / TITLE: - Association between the type and length of tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis.

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

REVISTA / JOURNAL: - J Drugs Dermatol. 2013 Aug 1;12(8):899-903.

AUTORES / AUTHORS: - Wu JJ; Poon KY; Bebchuk JD

RESUMEN / SUMMARY: - OBJECTIVE: We sought to assess whether the type of TNF inhibitor therapy (soluble receptor versus monoclonal antibody) has an effect on MI risk; and determine whether length of TNF inhibitor therapy has an effect on MI risk.
 DESIGN: Retrospective cohort study
 SETTING: Between January 1, 2004 and November 30, 2010
 PARTICIPANTS: At least 3 ICD9 codes for psoriasis (696.1) or psoriatic arthritis (696.0) (without antecedent MI).
 INTERVENTION: None
 MAIN OUTCOME MEASURE: Incident MI
 RESULTS: In the 3 subgroups of TNF inhibitors, 976 received etanercept; 217 received monoclonal antibody; and 480 received etanercept or monoclonal antibody, in addition, 5075 received topical therapy and 2097 received oral therapy. In the Cox proportional hazards analysis, etanercept (HR, 0.53; 95% CI, 0.31-0.92) was associated with a significant reduction of MI risk, compared to topical agents and, monoclonal antibody only (HR, 0.25; 95% CI, 0.06-1.03), and etanercept or monoclonal antibody (HR, 0.53; 95% CI, 0.27-1.06) were associated with a non-significant reduction of MI risk compared to topical agents. Using year 1 as reference, those who received TNF inhibitor therapy at year 2 (HR, 1.15; 95% CI, 0.30-4.44), at year 3 (HR, 1.89; 95% CI, 0.64-5.58), and at year 4 and above (HR, 1.16; 95% CI, 0.46-2.94) had a non-significant increase of MI risk.
 CONCLUSIONS: Treatment with etanercept, compared to treatment with topical agents, was associated with a significant decreased risk of MI in psoriasis patients. Treatment with monoclonal antibody and etanercept or monoclonal antibody, compared to treatment with topical agents, was associated with a non-significant decreased risk of MI risk in psoriasis patients. There were no statistically significant changes in risk of MI associated with length of TNF inhibitor treatment.

J Drugs Dermatol. 2013;12(8):899-903.

[634]

TÍTULO / TITLE: - The Prognostic Role of Ephrin A2 and Endothelial Growth Factor Receptor Pathway Mediators in Patients With Advanced Colorectal Cancer Treated With Cetuximab.

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

REVISTA / JOURNAL: - Clin Colorectal Cancer. 2013 Sep 16. pii: S1533-0028(13)00074-1. doi: 10.1016/j.clcc.2013.07.001.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clcc.2013.07.001](#)

AUTORES / AUTHORS: - Strimpakos A; Pentheroudakis G; Kotoula V; De Roock W; Kouvatsos G; Papakostas P; Makatsoris T; Papamichael D; Andreadou A; Sgouros J; Zizi-Sermpetzoglou A; Kominea A; Televantou D; Razis E; Galani E; Pectasides D; Tejpar S; Syrigos K; Fountzilias G

INSTITUCIÓN / INSTITUTION: - Oncology Unit, Third Department of Medicine, "Sotiria" General Hospital, Athens School of Medicine, Athens, Greece. Electronic address: alexstrimp@med.uoa.gr.

RESUMEN / SUMMARY: - BACKGROUND: Patients with colorectal cancer (CRC) with wild-type KRAS mutations are often treated with the endothelial growth factor receptor (EGFR) monoclonal antibody cetuximab. Despite the presence of a specific molecular target, most patients still do not derive benefit from this biological treatment. Our study explores the role of ephrin A2 (EphA2) receptor expression and of EGFR pathway mediators as predictors of cetuximab benefit. PATIENTS AND METHODS: Formalin-fixed paraffin-embedded (FFPE) tumor biopsy samples from 226 cetuximab-treated patients with CRC were studied for mRNA expression of insulin growth factor binding protein 2 (IGFBP2), insulin growth factor receptor 1 (IGF1R), cMET, EphA2, human epidermal growth factor receptor 2 (HER2), HER3, and HER4 by means of TaqMan reverse-transcribed polymerase chain reaction (RT-PCR). RESULTS: Of the 226 patients evaluable for exploratory analysis, 222 had complete data from follow-up visits. The univariate analysis revealed the following significant adverse prognostic factors for risk of death: high EphA2 mRNA levels (hazard ratio [HR], 1.61; P = .015), high HER2 mRNA levels (HR, 1.51; P = .045), and high IGF1R mRNA levels (HR, 1.56; P = .021). Low EphA2 tumor expression was significantly associated with objective response to cetuximab therapy. In multivariate analysis of a broad biomarker panel, factors with independent prognostic value included EphA2 mRNA levels (HR, 1.67; P = .029), high amphiregulin (AREG) mRNA levels in KRAS wild-type tumors (HR, 0.17; P < .0001), and high epiregulin (EREG) mRNA levels (HR, 0.38; P = .006). CONCLUSION: High EphA2 receptor expression in CRC was associated with a worse outcome in patients treated with cetuximab-based therapy. Prospective validation in treated and control patients is required to dissect the predictive from prognostic role in advanced CRC.

[635]

TÍTULO / TITLE: - Long-term outcomes and prognostic factors of patients with advanced gastric cancer treated with S-1 plus cisplatin combination chemotherapy as a first-line treatment.

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

REVISTA / JOURNAL: - Int J Clin Oncol. 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) 1007/s10147-013-0610-1

AUTORES / AUTHORS: - Kadowaki S; Komori A; Narita Y; Nitta S; Yamaguchi K; Kondo C; Taniguchi H; Takahari D; Ura T; Ando M; Muro K

INSTITUCIÓN / INSTITUTION: - Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi, 464-8681, Japan, skadowaki@aichi-cc.jp.

RESUMEN / SUMMARY: - BACKGROUND: The long-term outcomes of advanced gastric cancer (AGC) patients treated with S-1 plus cisplatin (SP) combination chemotherapy remain unclear. Therefore, we sought to evaluate these outcomes to identify the prognostic factors affecting patient survival. METHODS: We retrospectively analyzed 153 AGC patients treated with SP at a single institution between January 2005 and July 2011. RESULTS: Median overall survival (OS) was 15.0 months [95 % confidence interval (CI), 12.5-17.9 months]. Three independent prognostic factors affecting poor survival were identified: performance status (PS) ≥ 1 [hazard ratio (HR) = 2.39, 95 % CI, 1.58-3.62]; >1 metastatic site (HR = 1.57, 95 % CI, 1.10-2.26), and elevated alkaline phosphatase levels (HR = 1.70, 95 % CI, 1.16-2.49). A simple prognostic index was generated using three risk groups: good (no risk factor), moderate (one or two risk factors), and poor (three risk factors). The median OS for good-, moderate-, and poor-risk groups was 28.6, 14.8, and 7.3 months, respectively (log-rank test; $P < 0.0001$). Among the twelve 3-year survivors, 9 (75 %) had a PS of 0 and 8 (67 %) had only one metastatic site. CONCLUSIONS: Three prognostic factors were identified in AGC patients treated with SP. Using a simple prognostic index, the patients were divided into three risk groups, in which the survival differences were markedly significant, suggesting that patients with good PS and only one metastatic site may have a higher chance of long-term survival than those with poor PS and multiple metastatic sites.

[636]

TÍTULO / TITLE: - Simvastatin inhibits proliferation and induces apoptosis in human lung cancer cells.

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

REVISTA / JOURNAL: - Oncol Res. 2013;20(8):351-7. doi: 10.3727/096504013X13657689382897.

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

[3727/096504013X13657689382897](https://doi.org/10.3727/096504013X13657689382897)

AUTORES / AUTHORS: - Yu X; Pan Y; Ma H; Li W

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Yuhuangding Hospital, Yantai, Shandong, China. Xiaofeng273@yahoo.com.cn

RESUMEN / SUMMARY: - Lung cancer is the one of the most frequent causes of malignant tumors. In recent years, it has been documented that statins have anticancer and cancer chemopreventive properties. However, the mechanism of simvastatin on lung cancer is still unclear. In this study, the human lung cancer cell line A549 cells were incubated with simvastatin. Simvastatin inhibited the survival of A549 cells in a dose-dependent manner, decreased Bcl-2 protein expression, and increased Bax protein expression time and dose dependently. In addition, simvastatin blocked cells in the G1 phase of the cell cycle, downregulated cyclin D1 and CDKs protein expression, mediated the mitochondria-dependent caspase cascade by increasing caspase-3, -8, and -9 mRNA and protein expression, downregulated Xiap levels to induce cells apoptosis. Importantly, simvastatin suppressed decreased MMP-9 protein expression and suppressed NF-kappaB activation in A549 cells. Taken together, these results showed that the anticancer effect of simvastatin in lung cancer A549 cells via the inhibiting cell proliferation, influencing the cell cycle, downregulating cyclin D1 and CDKs expression, inducing apoptosis, and decreasing MMP-9 levels, possibly by inhibiting the activation of NF-kappaB. Statins contribute to lung cancer therapy and may be an ideal anticancer and cancer chemopreventive agent for lung cancer.

[637]

TÍTULO / TITLE: - Protein kinase inhibitors in metastatic colorectal cancer. Let's pick patients, tumors, and kinase inhibitors to piece the puzzle together!

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

REVISTA / JOURNAL: - Expert Opin Pharmacother. 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1517/14656566.2013.828694](https://doi.org/10.1517/14656566.2013.828694)

AUTORES / AUTHORS: - Stintzing S; Lenz HJ

INSTITUCIÓN / INSTITUTION: - Keck School of Medicine, USC/Norris Comprehensive Cancer Center, Sharon Carpenter Laboratory, 1441 Eastlake Avenue, Room 3456, Los Angeles, CA 90033, USA lenz@usc.edu.

RESUMEN / SUMMARY: - Introduction: Increased understanding in intracellular signaling pathways leading to carcinogenesis, proliferation, migration, invasion, angiogenesis, and anti-apoptosis of colorectal cancer cells has been critical for target identification and drug development. Specific protein kinase inhibitors (KIs) have been developed to block activated pathways associated with tumor growth and progression. Although showing promising activity in preclinical models, until now, the majority of KIs were not able to demonstrate clinically meaningful efficacy in Phase II/III trials. Areas

covered: The major pathways altered in colorectal cancer will be highlighted, and molecularly defined targets will be discussed. The mechanisms of action and the proof of principle demonstrated in preclinical models of KIs and the disappointing efficacy in clinical trials will be reviewed. Expert opinion: Despite recent negative study results, KIs have the potential to be the next class of therapeutics in the treatment of metastatic colorectal cancer. Molecular classification of the individual tumors and identification of molecular escape mechanisms for primary (intrinsic) and secondary resistances to KI treatment is critical to select the patients' most likely to benefit. Appropriate drug combinations based on those mechanisms of resistance have to be tested in selected patient populations to ensure progress and efficacy with the goal to lead to a clinically meaningful prolongation of patients' lives.

[638]

TÍTULO / TITLE: - p19 mRNA and protein expression as new prognostic factors in ovarian cancer patients.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 14;14(10).

AUTORES / AUTHORS: - Felisiak-Golabek A; Dansonka-Mieszkowska A; Rzepecka IK; Szafron L; Kwiatkowska E; Konopka B; Podgorska A; Rembiszewska A; Kupryjanczyk J

INSTITUCIÓN / INSTITUTION: - Department of Pathology; The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology; Warsaw, Poland.

RESUMEN / SUMMARY: - p19INK4d (CDKN2D) is a negative regulator of the cell cycle. Little is known of its role in cancer development and prognosis. We aimed to evaluate the clinical significance of p19INK4d expression in ovarian carcinomas with respect to the TP53 accumulation status, as well as the frequency of CDKN2D mutations. p19INK4d and TP53 expression was evaluated immunohistochemically in 445 ovarian carcinomas: 246 patients were treated with platinum-cyclophosphamide (PC/PAC), while 199 were treated with taxane-platinum agents (TP). CDKN2D gene expression (mRNA) was examined in 106 carcinomas, while CDKN2D mutations in 68 tumors. Uni- and multivariate statistical analyses (logistic regression and the Cox proportional hazards model) were performed for patient groups divided according to the chemotherapeutic regimen administered, and in subgroups with and without TP53 accumulation. High p19INK4d expression increased the risk of death, but only in patients with the TP53-negative carcinomas (HR 1.61, P = 0.049 for PC/PAC-treated patients, HR 2.00, P = 0.015 for TP-treated patients). This result was confirmed by the mRNA analysis (HR 4.24, P = 0.001 for TP-treated group). High p19INK4d protein expression associated with adverse clinicopathological factors. We found no alterations in the CDKN2D gene; the c.90C>G (p.R30R; rs1968445) polymorphism was detected in 10% of tumors. Our results suggest that p19INK4d expression is a poor

prognostic factor in ovarian cancer patients. Analyses of tumor groups according to the TP53 accumulation status facilitate the identification of cancer biomarkers.

[639]

TÍTULO / TITLE: - Glyceraldehyde-3-phosphate dehydrogenase gene over expression correlates with poor prognosis in non small cell lung cancer patients.

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

REVISTA / JOURNAL: - Mol Cancer. 2013 Aug 29;12(1):97.

●● Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-97](#)

AUTORES / AUTHORS: - Puzone R; Savarino G; Salvi S; Dal Bello MG; Barletta G; Genova C; Rijavec E; Sini C; Esposito AI; Ratto GB; Truini M; Grossi F; Pfeffer U

RESUMEN / SUMMARY: - BACKGROUND: Glycolysis in presence of oxygen with high glucose consumption is known to be the metabolism of choice in many tumors. In lung cancer this phenomenon is routinely exploited in diagnostic PET imaging of fluorodeoxyglucose uptake, but not much is known about the prognostic capabilities of glycolysis level assessment in resected lung tumor samples. METHODS: In this retrospective study, we used real time polymerase chain reaction(RQ-PCR) to assess the expression level of the gene for Glyceraldehyde 3-phosphate dehydrogenase(GAPDH), key enzyme for glucose breakdown, in tumor samples from 82 consecutive early stages resected non small cell lung cancer(NSCLC) patients. We then compared our results in six large publicly available NSCLC microarray datasets collecting data from over 1250 total patients. RESULTS: In our study GAPDH gene over expression was found to be an adverse prognostic factor in early stages NSCLC (n = 82 HR = 1.30 p = 0.050). This result was confirmed in 5 of 6 public datasets analyzed: Shedden et al. 2008: n = 442 HR = 1.54 p < 0.0001; Lee et al. 2008: n = 138 HR = 1.31 p = 0.043; Tomida et al. 2009: n = 117 HR = 1.59 p = 0.004; Roepman et al. 2009: n = 172 (TP11 gene) HR = 1.51 p = 0.009; Okayama et al. 2012: n = 226 HR = 3.19 p < 0.0001; Botling et al. 2013: n = 196 HR = 1.00 p = 0.97). Furthermore, in the large and clinically well annotated Shedden et al. microarray dataset, GAPDH hazard ratio did not change whether calculated for the whole dataset or for the subgroup of adjuvant naive patients only (n = 330 HR = 1.49 p < 0.0001). CONCLUSION: GAPDH gene over expression in resected tumor samples is an adverse prognostic factor in NSCLC. Our results confirm the prognostic value of glucose metabolism assessment in NSCLC.

[640]

TÍTULO / TITLE: - Prognostic factors and outcomes of unrelated bone marrow transplantation for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) pre-treated with tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Osaka City Med J. 2013 Jun;59(1):9-21.

AUTORES / AUTHORS: - Yoshimura T; Nakane T; Hirose A; Koh H; Nakamae M; Aimoto M; Nishimoto M; Hayashi Y; Terada Y; Nakamae H; Hino M

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Osaka City University, Graduate School of Medicine, Japan.

RESUMEN / SUMMARY: - **BACKGROUND:** The treatment and prognosis of Acute Lymphoblastic Leukemia (ALL), including Philadelphia chromosome positive ALL (Ph+ALL), a poor prognostic factor, has changed with the introduction of tyrosine kinase inhibitors (TKIs). Nevertheless, allogeneic hematopoietic cell transplantation (allo-HCT) is still recommended as the first-line curative treatment. To date, no study has investigated the prognostic factors and outcomes of unrelated bone marrow transplantation (u-BMT) for Ph+ALL following pre-transplant treatment with a TKI-containing regimen. **METHODS:** We retrospectively evaluated 15 transplantations of 14 patients with Ph+ALL pre-treated with a TKI-containing regimen at our institute. The 14 patients comprised 11 males and 3 females, with a median age of 50 years (range: 19-64). We performed univariate and multivariate analyses of risk factors that contributed to overall survival (OS) or leukemia-free survival (LFS). **RESULTS:** Three-year OS of the patients with molecular complete remission (MCR) and with non-MCR at transplantation were 89% and 40% ($p = 0.006$), respectively, and three-year LFS rates were 79% and 0% ($p = 0.001$), respectively. Univariate analysis revealed that first hematological complete remission (HCR1) and MCR at transplant were significantly related to better OS and LFS. Multivariate analysis showed that MCR at transplant was significantly associated with better OS and LFS. **CONCLUSIONS:** In agreement with a previous study that included other stem cell sources, u-BMT was deemed feasible for the treatment of Ph+ALL. Analysis of a larger cohort is required to clarify the prognostic factors that affect transplant outcome in Ph+ALL since the introduction of TKIs.

[641]

TÍTULO / TITLE: - Prognostic Significance of Human Papillomavirus (HPV) Status and Expression of Selected Markers (HER2/neu, EGFR, VEGF, CD34, p63, p53 and Ki67/MIB-1) on Outcome After (Chemo-) Radiotherapy in Patients with Squamous Cell Carcinoma of Uterine Cervix.

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

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Aug 3.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12253-013-9674-5](#)

AUTORES / AUTHORS: - Vosmik M; Laco J; Sirak I; Beranek M; Hovorkova E; Vosmikova H; Drastikova M; Hodek M; Zoul Z; Odrazka K; Petera J

INSTITUCIÓN / INSTITUTION: - Department of Oncology and Radiotherapy, University Hospital Hradec Kralove, Sokolska 581, 500 05, Hradec Kralove, Czech Republic, milan.vosmik@fnhk.cz.

RESUMEN / SUMMARY: - The aim of the retrospective study was to evaluate prognostic significance of human papillomavirus (HPV) status and expression of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor type 2 (HER2/neu), vascular endothelial growth factor (VEGF), CD34 antigen, tumor suppressors p63 and p53, and Ki67/MIB-1 in squamous cell carcinoma of the uterine cervix (SCCC) treated with radiotherapy or chemoradiotherapy. Seventy-two consecutive patients with SCCC, diagnosed and treated with (chemo-) radiotherapy with a curative intent at the University Hospital Hradec Kralove between August 1998 and August 2008, were enrolled in the study. The median follow-up period was 57 months (range 5-152). The tested biological factors were evaluated by polymerase chain reaction (HPV status) and by immunohistochemistry (remaining above mentioned markers) from archival paraffin embedded original diagnostic tumor samples. A statistical significant correlation was observed between low expression of p63 and poor overall survival ($p = 0.001$), although the complete response probability was influenced with borderline statistical significance ($p = 0.05$). However, the results could be affected by the statistical error due to the small number of p63 negative patients. HPV positivity and EGFR staining intensity was associated with higher complete response probability ($p = 0.038$ and $p = 0.044$, resp.). All other results were not significant. Neither HPV positivity nor EGFR staining intensity were reflected in the overall survival evaluation. In conclusion, the presented study did not confirm any apparently significant association of the suggested markers with prognosis of SCCC in patients treated with (chemo-) radiotherapy.

[642]

TÍTULO / TITLE: - Identification of a KRAS mutation in a patient with non-small cell lung cancer treated with chemoradiotherapy and panitumumab.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 2;14(10).

AUTORES / AUTHORS: - Zaorsky NG; Sun Y; Wang Z; Palmer J; Fortina PM; Solomides C; Werner-Wasik M; Dicker AP; Axelrod R; Campling B; Evans N; Cowan S; Lu B

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology; Fox Chase Cancer Center; Philadelphia, PA USA.

RESUMEN / SUMMARY: - RTOG 0839 is a Phase II study of pre-operative chemoradiotherapy with or without panitumumab in potentially operable locally advanced non-small cell lung cancer (NSCLC). The investigational agent, panitumumab, is an anti-epithelial growth factor receptor (EGFR) antibody that improves progression-free survival in chemorefractory metastatic colorectal cancer (mCRC). Recently, both

KRAS mutational status (i.e., mutated or not) and subtype (i.e., activating or inactivating) have been shown to be predictive of response to anti-EGFR therapy in mCRC. However, in NSCLC, it is unknown if KRAS mutational status or subtype predict benefit to anti-EGFR therapies because of unique genetic and epigenetic factors unique to each cancer. We present a patient with stage III NSCLC containing a KRAS G12D activating mutation who had a partial pathologic response, with disappearance of a minor KRAS mutant clone. This case suggests possible eradication of the G12D KRAS lung cancer clones by concurrent chemoradiation with panitumumab.

[643]

TÍTULO / TITLE: - The translocation t(2;11)(p21;q23) without MLL gene rearrangement-a possible marker of good prognosis in myelodysplastic syndrome patients.

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

REVISTA / JOURNAL: - Hematol Oncol. 2013 Aug 16. doi: 10.1002/hon.2089.

●● [Enlace al texto completo \(gratis o de pago\) 1002/hon.2089](#)

AUTORES / AUTHORS: - Dvorak P; Lysak D; Vokurka S; Michalova K; Sarova I; Jonasova A; Hrubá M; Rykowska A; Subrt I

INSTITUCIÓN / INSTITUTION: - Institute of Medical Genetics, University Hospital Pilsen, Pilsen, Czech Republic.

RESUMEN / SUMMARY: - The translocation t(2;11)(p21;q23) is associated with de novo myelodysplastic syndromes (MDS) and has an overall frequency of approximately 1%. The outcome of MDS patients with this translocation is not clear until now, because most of the clinical data addressing the t(2;11)(p21;q23) has been collected without investigating the status of the mixed lineage leukemia (MLL) gene. In this report, we present seven new patients with MDS diagnosis and the t(2;11)(p21;q23) in bone marrow cells; all of them without MLL gene rearrangement. They were found in two databases consisting of 1185 patients of two Czech institutions. These patients tended to be younger and showed a strong male predominance. A cytological and histological assessment of bone marrow at diagnosis revealed only mild MDS with marked dysplasia in megakaryopoiesis. Similar to other primary abnormalities in MDS (e.g. deletion of 11q), the t(2;11)(p21;q23) was frequently associated with deletion of 5q. Our results stress the common clinicopathological features of this entity and indicate that the t(2;11)(p21;q23) may be associated with a good prognosis for MDS patients (median survival 72 months). Copyright © 2013 John Wiley & Sons, Ltd.

[644]

TÍTULO / TITLE: - The association between neutropenia and prognosis in stage III colorectal cancer patients receiving adjuvant chemotherapy.

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

REVISTA / JOURNAL: - Eur J Cancer Care (Engl). 2013 Sep 4. doi: 10.1111/ecc.12120.

●● Enlace al texto completo (gratis o de pago) [1111/ecc.12120](https://doi.org/10.1111/ecc.12120)

AUTORES / AUTHORS: - Sunaga T; Suzuki S; Kogo M; Kurihara T; Kaji S; Koike N; Harada N; Suzuki M; Kiuchi Y

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Hachioji Digestive Disease Hospital, Tokyo, Japan; Department of Pharmacy Education, Showa University School of Pharmacy, Tokyo, Japan.

RESUMEN / SUMMARY: - Neutropenia during chemotherapy has been reported to be a predictor of better survival in patients with several types of cancer, although there are no reports on stage III colorectal cancer (CRC). The purpose of this study was to examine the association between neutropenia and prognosis in stage III CRC patients receiving adjuvant chemotherapy consisting of oral uracil and tegafur (UFT) plus leucovorin (LV). We retrospectively analysed 123 patients with stage III CRC who received UFT/LV as adjuvant chemotherapy. The end-point was disease-free survival (DFS). Survival curves of the two categories (neutropenia absent vs. present) were estimated using the Kaplan-Meier method and compared by the log-rank test. We estimated the hazard ratio (HR) for DFS according to neutropenia after adjustment for covariates by multivariate analyses using Cox's regression analysis. A total of 33 (26.8%) patients experienced neutropenia. Patients without neutropenia showed a significantly lower DFS than those with neutropenia (3-year DFS 57.3% vs. 81.2%, $P = 0.0213$). By multivariate analysis, neutropenia and histological type were independent prognostic factors, with HR of 0.410 (neutropenia absent vs. present, $P = 0.045$) and 4.793 (well to moderately differentiated vs. poorly differentiated, $P = 0.004$) respectively. We demonstrated that neutropenia occurring during adjuvant chemotherapy consisting of UFT/LV may be a prognostic factor of recurrence in stage III CRC patients.

[645]

TÍTULO / TITLE: - A genome-wide association study of chemotherapy-induced alopecia in breast cancer patients.

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

REVISTA / JOURNAL: - Breast Cancer Res. 2013 Sep 11;15(5):R81.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3475](https://doi.org/10.1186/bcr3475)

AUTORES / AUTHORS: - Chung S; Low SK; Zembutsu H; Takahashi A; Kubo M; Sasa M; Nakamura Y

RESUMEN / SUMMARY: - INTRODUCTION: Chemotherapy-induced alopecia is one of the most common adverse events caused by conventional cytotoxic chemotherapy, yet there has been very little progress in the prevention or treatment of this side effect. Although this is not a life-threatening event, alopecia is very psychologically difficult for many women to manage. In order to improve the quality of life for these women, it

is important to elucidate the molecular mechanisms of chemotherapy-induced alopecia and develop ways to effectively prevent and/or treat it. To identify the genetic risk factors associated with chemotherapy-induced alopecia, we conducted a genome-wide association study (GWAS) using DNA samples from breast cancer patients who were treated with chemotherapy. METHODS: We performed case—control association study of 303 individuals who developed grade 2 alopecia, and compared them with 880 breast cancer patients who did not show hair loss after being treated with conventional chemotherapy. In addition, we separately analyzed a subset of patients who received specific combination therapies by GWASs and applied the weighted genetic risk scoring (wGRS) system to investigate the cumulative effects of the associated SNPs. RESULTS: We identified a SNP significantly associated with drug-induced grade 2 alopecia (rs3820706 in CACNB4 (calcium channel voltage-dependent subunit beta 4) on 2q23, $P = 8.13 \times 10^{-9}$, OR = 3.71) and detected several SNPs, which showed some suggestive associations by subgroup analyses. We also classified patients into four groups on the basis of wGRS analysis and found that patients who classified in the highest risk group showed 443 times higher risk of anti-microtubule agents-induced alopecia than the lowest risk group. CONCLUSIONS: Our study suggests several associated genes and should shed some light on the molecular mechanism of alopecia in chemotherapy-treated breast cancer patients and hopefully will contribute to development of interventions that will improve the quality of life (QOL) of cancer patients.

[646]

TÍTULO / TITLE: - RRM1 and RRM2 pharmacogenetics: association with phenotypes in HapMap cell lines and acute myeloid leukemia patients.

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

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Sep;14(12):1449-66. doi: 10.2217/pgs.13.131.

●● [Enlace al texto completo \(gratuito o de pago\) 2217/pgs.13.131](#)

AUTORES / AUTHORS: - Cao X; Mitra AK; Pounds S; Crews KR; Gandhi V; Plunkett W; Dolan ME; Hartford C; Raimondi S; Campana D; Downing J; Rubnitz JE; Ribeiro RC; Lamba JK

INSTITUCIÓN / INSTITUTION: - Department of Biostatistics, St Jude Children's Research Hospital, Memphis, TN, USA.

RESUMEN / SUMMARY: - Background: Ribonucleotide reductase catalyzes an essential step in the cellular production of deoxyribonucleotide triphosphates and has been associated with clinical outcome in cancer patients receiving nucleoside analog-based chemotherapy. Materials & methods: In the current study, we sequenced the genes RRM1 and RRM2 in genomic DNA from HapMap cell lines with European (Utah residents with northern and western European ancestry [CEU]; n = 90) or African

(Yoruba people in Ibadan, Nigeria [YRI]; n = 90) ancestry. Results: We identified 44 genetic variants including eight coding SNPs in RRM1 and 15 SNPs including one coding SNP in RRM2. RRM1 and RRM2 mRNA expression levels were significantly correlated with each other in both CEU and YRI lymphoblast cell lines, and in leukemic blasts from acute myeloid leukemia (AML) patients (AML97, n = 89; AML02, n = 187). Additionally, RRM1 expression was higher among patient features indicative of a high relapse hazard. We evaluated SNPs within the RRM1 and RRM2 genes in the HapMap lymphoblast cell lines from CEU and YRI panels for association with expression and cytarabine chemosensitivity. SNPs of potential significance were further evaluated in AML patients. RRM1 SNPs rs1042919 (which occurs in linkage disequilibrium with multiple other SNPs) and promoter SNP rs1561876 were associated with intracellular 1-beta-d-arabinofuranosyl-CTP levels, response after remission induction therapy, risk of relapse and overall survival in AML patients receiving cytarabine and cladribine. Conclusion: These results suggest that SNPs within ribonucleotide reductase might be helpful predictive markers of response to nucleoside analogs and should be further validated in larger cohorts. Original submitted 2 April 2013; Revision submitted 8 July 2013.

[647]

TÍTULO / TITLE: - Irreversible hepatotoxicity after administration of trabectedin to a pleiomorphic sarcoma patient with a rare ABCC2 polymorphism: a case report.

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

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Sep;14(12):1389-96. doi: 10.2217/pgs.13.124.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.124](#)

AUTORES / AUTHORS: - Laurenty AP; Thomas F; Chatelut E; Betrian S; Guellec CL; Hennebelle I; Guellec SL; Chevreau C

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Institut Claudius Regaud, Toulouse, France.

RESUMEN / SUMMARY: - We describe here the case of a 60-year old male patient treated for an extensive local progression of a pleiomorphic sarcoma on the right tibial crest with second-line trabectedin. Two cycles were administered before a major liver toxicity was retrieved, with both cytolytic and cholestatic hepatitis quickly associated with irreversible jaundice. The radiological, histological, chemistry and pharmacogenetic investigations led us to diagnose chronic hepatobiliary toxicity with portal fibrosis, cholangiolitis damages and chronic hepatopathy. The patient had a deficient variant genotype of ABCC2 (c.-24TT, c.4488CT and c.4544GA), which has been suggested to play a role in excretion of toxic metabolites of trabectedin. This case report is, to our knowledge, the first description of trabectedin's irreversible liver toxicity in a human patient. Supported by a thorough review of the literature, this

hepatitis is thought to have resulted from a multihit process involving genetic variants of ABC proteins and comedication.

[648]

TÍTULO / TITLE: - Expression profiling of ion channel genes predicts clinical outcome in breast cancer.

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

REVISTA / JOURNAL: - Mol Cancer. 2013 Sep 22;12(1):106.

●● Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-106](#)

AUTORES / AUTHORS: - Ko JH; Ko EA; Gu W; Lim I; Bang H; Zhou T

RESUMEN / SUMMARY: - BACKGROUND: Ion channels play a critical role in a wide variety of biological processes, including the development of human cancer. However, the overall impact of ion channels on tumorigenicity in breast cancer remains controversial. METHODS: We conduct microarray meta-analysis on 280 ion channel genes. We identify candidate ion channels that are implicated in breast cancer based on gene expression profiling. We test the relationship between the expression of ion channel genes and p53 mutation status, ER status, and histological tumor grade in the discovery cohort. A molecular signature consisting of ion channel genes (IC30) is identified by Spearman's rank correlation test conducted between tumor grade and gene expression. A risk scoring system is developed based on IC30. We test the prognostic power of IC30 in the discovery and seven validation cohorts by both Cox proportional hazard regression and log-rank test. RESULTS: 22, 24, and 30 ion channel genes are found to be differentially expressed with a change in p53 mutation status, ER status, and tumor histological grade in the discovery cohort. We assign the 30 tumor grade associated ion channel genes as the IC30 gene signature. We find that IC30 risk score predicts clinical outcome ($P < 0.05$) in the discovery cohort and 6 out of 7 validation cohorts. Multivariate and univariate tests conducted in two validation cohorts indicate that IC30 is a robust prognostic biomarker, which is independent of standard clinical and pathological prognostic factors including patient age, lymph node status, tumor size, tumor grade, estrogen and progesterone receptor status, and p53 mutation status. CONCLUSIONS: We identified a molecular gene signature IC30, which represents a promising diagnostic and prognostic biomarker in breast cancer. Our results indicate that information regarding the expression of ion channels in tumor pathology could provide new targets for therapy in human cancers.

[649]

TÍTULO / TITLE: - Phase II study of cilengitide in the treatment of refractory or relapsed high-grade gliomas in children: A report from the Children's Oncology Group.

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

REVISTA / JOURNAL: - Neuro Oncol. 2013 Oct;15(10):1438-44. doi: 10.1093/neuonc/not058. Epub 2013 Sep 5.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not058](https://doi.org/10.1093/neuonc/not058)

AUTORES / AUTHORS: - Macdonald TJ; Vezina G; Stewart CF; Turner D; Pierson CR; Chen L; Pollack IF; Gajjar A; Kieran MW

INSTITUCIÓN / INSTITUTION: - Corresponding Author: Tobey J. MacDonald, MD, Emory Children's Center, Aflac Cancer and Blood Disorders Center, 2015 Uppergate Drive NE, Suite 442, Atlanta, GA 30322. tobey.macdonald@emory.edu.

RESUMEN / SUMMARY: - Background Cilengitide, an alphav integrin antagonist, has demonstrated activity in recurrent adult glioblastoma (GBM). The Children's Oncology Group ACNS0621 study thus evaluated whether cilengitide is active as a single agent in the treatment of children with refractory high-grade glioma (HGG). Secondary objectives were to investigate the pharmacokinetics and pharmacogenomics of cilengitide in this population. Methods Cilengitide (1800 mg/m²/dose intravenous) was administered twice weekly until evidence of disease progression or unacceptable toxicity. Thirty patients (age range, 1.1-20.3 years) were enrolled, of whom 24 were evaluable for the primary response end point. Results Toxicity was infrequent and mild, with the exception of one episode of grade 2 pain possibly related to cilengitide. Two intratumoral hemorrhages were reported, but only one (grade 2) was deemed to be possibly related to cilengitide and was in the context of disease progression. One patient with GBM received cilengitide for 20 months and remains alive with continuous stable disease. There were no other responders, with median time to tumor progression of 28 days (range, 11-114 days). Twenty-one of the 24 evaluable patients died, with a median time from enrollment to death of 172 days (range, 28-325 days). The 3 patients alive at the time of this report had a follow-up time of 37, 223, and 1068 days, respectively. Conclusions We conclude that cilengitide is not effective as a single agent for refractory pediatric HGG. However, further study evaluating combination therapy with cilengitide is warranted before a role for cilengitide in the treatment of pediatric HGG can be excluded.

[650]

TÍTULO / TITLE: - Posttreatment prognostic nomogram for patients with metastatic urothelial cancer completing first-line cisplatin-based chemotherapy.

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

REVISTA / JOURNAL: - Urol Oncol. 2013 Sep 18. pii: S1078-1439(13)00288-3. doi: 10.1016/j.urolonc.2013.07.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.urolonc.2013.07.001](https://doi.org/10.1016/j.urolonc.2013.07.001)

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

INSTITUCIÓN / INSTITUTION: - The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY. Electronic address: matthew.galsky@mssm.edu.

RESUMEN / SUMMARY: - BACKGROUND: Models to predict the outcome of patients with metastatic urothelial cancer (UC), based on pretreatment variables, have previously been developed. However, patients often request “updated” prognostic estimates based upon their response to treatment. PATIENTS AND METHODS: Data were pooled from 317 patients enrolled in 8 trials evaluating first-line cisplatin-based chemotherapy in metastatic UC. Variables were combined in the Cox proportional hazards model to produce a nomogram to predict survival from the end of treatment. The nomogram was validated externally using data from a phase III trial. RESULTS: The median survival from end of treatment was 10.65 months (95% confidence interval; 9.20-13.24); 69% of patients had died. Baseline and posttreatment variables were evaluated. Baseline performance status, baseline number of visceral metastatic sites, baseline white blood counts, and response to treatment were included in the final model. The nomogram achieved a bootstrap-corrected concordance index of 0.68. Upon external validation, the nomogram achieved a concordance index of 0.67. CONCLUSIONS: A model derived from pretreatment and posttreatment variables was constructed to predict survival from the completion of first-line chemotherapy in patients with metastatic UC. This model may be useful for patient counseling and for stratification of trials exploring “maintenance” therapy.

[651]

TÍTULO / TITLE: - Clinical investigation of receptor and non-receptor tyrosine kinase inhibitors for the treatment of epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Expert Opin Pharmacother. 2013 Aug 12.

- [Enlace al texto completo \(gratis o de pago\) 1517/14656566.2013.826650](#)

AUTORES / AUTHORS: - Klempner SJ; Myers AP; Mills GB; Westin SN

INSTITUCIÓN / INSTITUTION: - Beth Israel Deaconess Medical Center, Division of Hematology-Oncology, Boston, MA 02215, USA.

RESUMEN / SUMMARY: - Introduction: Epithelial ovarian cancer (EOC) is the second most common gynecologic malignancy and the leading cause of death from gynecologic cancer in the USA. EOC is an exquisitely chemo-sensitive disease with response rates of over 75% in the upfront setting. Despite this, due to high rates of recurrence and development of chemo-resistance, the overall survival of EOC remains about 25%. Thus, there is a great need for new therapeutic approaches to render more durable responses. Based on preclinical and early phase clinical studies, key targeted pathways include targets that drive angiogenesis and chemo-resistance. Receptor tyrosine kinases and non-receptor tyrosine kinases play important roles in these processes and several small molecule tyrosine kinase inhibitors (TKIs) are in clinical development.

Areas covered: This review summarizes clinical rationale, mechanisms of action and clinical data for the TKIs under evaluation in the Phase III setting for EOC. Expert opinion: Despite reasonable preclinical activity, small molecule TKIs are unlikely to improve patient survival as single agent therapies in an unselected EOC population. Incorporation of tissue evaluation during ongoing clinical trials is required to identify molecularly defined groups that respond to single agents and direct rational combination strategies based on mechanisms of resistance to improve outcomes in EOC.

[652]

TÍTULO / TITLE: - Targeting inhibitor 2 of protein phosphatase 2^a as a therapeutic strategy for prostate cancer treatment.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 5;14(10).

AUTORES / AUTHORS: - Mukhopadhyay A; Tabanor K; Chaguturu R; Aldrich JV

INSTITUCIÓN / INSTITUTION: - Higuchi Biosciences Center; The University of Kansas; Lawrence, KS USA.

RESUMEN / SUMMARY: - Inhibitor 2 of protein phosphatase 2^a (I2PP2A), a biological inhibitor of the cellular serine/threonine protein phosphatase PP2A, is associated with numerous cellular processes that often lead to the formation and progression of cancer. In this study we hypothesized that targeting the inhibition of I2PP2A's multiple functions in prostate cancer cells might prevent cancer progression. We have investigated the effect of the small chain C6-ceramide, known to be a bioactive tumor suppressor lipid, on I2PP2A function, thereby affecting c-Myc signaling and histone acetylation in cells. Our data indicated that C6-ceramide treatment of prostate cancer cells induces cell death in PC-3, DU145, and LNCaP cells, but not normal prostate epithelial cells. C6-ceramide was able to disrupt the association between PP2A and I2PP2A. C6-ceramide inhibits I2PP2A's upregulation of c-Myc and downregulation of histone acetylation in prostate cancer cells. Our data indicated that targeting cancer related signaling pathways through I2PP2A using ceramide as an anti-I2PP2A agent could have beneficial effects as a therapeutic approach to prevent prostate cancer.

[653]

TÍTULO / TITLE: - Estrogen receptor alpha/beta ratio and estrogen receptor beta as predictors of endocrine therapy responsiveness—a randomized neoadjuvant trial comparison between anastrozole and tamoxifen for the treatment of postmenopausal breast cancer.

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

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 18;13(1):425.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-425](https://doi.org/10.1186/1471-2407-13-425)

AUTORES / AUTHORS: - Madeira M; Mattar A; Logullo AF; Soares FA; Gebrim LH

RESUMEN / SUMMARY: - BACKGROUND: The role of estrogen receptor beta (ER-beta) in breast cancer (BC) remains unclear. Some studies have suggested that ER-beta may oppose the actions of estrogen receptor alpha (ER-alpha), and clinical evidence has indicated that the loss of ER-beta expression is associated with a poor prognosis and resistance to endocrine therapy. The objective of the present study was to determine the role of ER-beta and the ER-alpha/ER-beta ratio in predicting the response to endocrine therapy and whether different regimens have any effect on ER-beta expression levels. METHODS: Ninety postmenopausal patients with primary BC were recruited for a short-term double-blinded randomized prospective controlled study. To determine tumor cell proliferation, we measured the expression of Ki67 in tumor biopsy samples taken before and after 26 days of treatment with anastrozole 1 mg/day (N = 25), tamoxifen 20 mg/day (N = 24) or placebo (N = 29) of 78 participants. The pre- and post-samples were placed in tissue microarray blocks and submitted for immunohistochemical assay. Biomarker statuses (ER-beta, ER-alpha and Ki67) were obtained by comparing each immunohistochemical evaluation of the pre- and post-surgery samples using the semi-quantitative Allred's method. Statistical analyses were performed using an ANOVA and Spearman's correlation coefficient tests, with significance at $p \leq 0.05$. RESULTS: The frequency of ER-beta expression did not change after treatment ($p = 0.33$). There were no significant changes in Ki67 levels in ER-beta-negative cases ($p = 0.45$), but in the ER-beta-positive cases, the anastrozole ($p = 0.01$) and tamoxifen groups ($p = 0.04$) presented a significant reduction in post-treatment Ki67 scores. There was a weak but positive correlation between the ER-alpha and ER-beta expression levels. Only patients with an ER-alpha/ER-beta expression ratio between 1 and 1.5 demonstrated significant differences in Ki67 levels after treatment with anastrozole ($p = 0.005$) and tamoxifen ($p = 0.026$). CONCLUSIONS: Our results provide additional data that indicate that the measurement of ER-beta in BC patients may help predict tamoxifen and anastrozole responsiveness in the neoadjuvant setting. These effects of hormonal treatment appear to be dependent on the ratio of ER-alpha/ER-beta expression. Trial registration: Current Controlled Trials ISRCTN89801719.

[654]

TÍTULO / TITLE: - Therapeutic drug management of BCR-ABL tyrosine kinase inhibitor for chronic myeloid leukemia patients.

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

REVISTA / JOURNAL: - Rinsho Ketsueki. 2013 Oct;54(10):1720-9.

AUTORES / AUTHORS: - Miura M; Takahashi N

[655]

TÍTULO / TITLE: - Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting BRCA mutation carrier probabilities: A retrospective study in a sample of Italian cancer genetics clinics.

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

REVISTA / JOURNAL: - Breast. 2013 Sep 4. pii: S0960-9776(13)00229-4. doi: 10.1016/j.breast.2013.07.053.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.07.053](#)

AUTORES / AUTHORS: - Varesco L; Viassolo V; Viel A; Gismondi V; Radice P; Montagna M; Alducci E; Della Puppa L; Oliani C; Tommasi S; Caligo MA; Vivinet C; Zuradelli M; Mandich P; Tibiletti MG; Cavalli P; Lucci Cordisco E; Turchetti D; Boggiani D; Bracci R; Bruzzi P; Bonelli L

INSTITUCIÓN / INSTITUTION: - Unit of Hereditary Cancer, IRCCS AOU San Martino - IST, Largo Rosanna Benzi, 10, 16132 Genoa, Italy. Electronic address: liliana.varesco@hsanmartino.it.

RESUMEN / SUMMARY: - **PURPOSE:** To evaluate in current practice the performance of BOADICEA and BRCAPRO risk models and empirical criteria based on cancer family history for the selection of individuals for BRCA genetic testing. **PATIENTS AND METHODS:** The probability of BRCA mutation according to the three tools was retrospectively estimated in 918 index cases consecutively undergone BRCA testing at 15 Italian cancer genetics clinics between 2006 and 2008. **RESULTS:** 179 of 918 cases (19.5%) carried BRCA mutations. With the strict use of the criteria based on cancer family history 173 BRCA (21.9%) mutations would have been detected in 789 individuals. At the commonly used 10% threshold of BRCA mutation carrier probability, the genetic models showed a similar performance [PPV (38% and 37%), sensitivity (76% and 77%) and specificity (70% and 69%)]. Their strict use would have avoided around 60% of the tests but would have missed approximately 1 every 4 carriers. **CONCLUSION:** Our data highlight the complexity of BRCA testing referral in routine practice and question the strict use of genetic models for BRCA risk assessment.

[656]

TÍTULO / TITLE: - Grb14 as an Independent Good Prognosis Factor for Breast Cancer Patients Treated with Neoadjuvant Chemotherapy.

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

REVISTA / JOURNAL: - Jpn J Clin Oncol. 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1093/jco/hyt130](#)

AUTORES / AUTHORS: - Huang O; Jiang M; Zhang X; Xie Z; Chen X; Wu J; Liu H; Shen K

INSTITUCIÓN / INSTITUTION: - 1Department of Surgery, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai.

RESUMEN / SUMMARY: - OBJECTIVE: Growth factor receptor-binding protein 14, a new member of noncatalytic adaptor proteins family, has been shown to be upregulated in breast cancer. We investigated the prognostic value of growth factor receptor-binding protein 14 expression in breast cancer patients treated with neoadjuvant chemotherapy. METHODS: Primary breast cancer specimens were taken from locally advanced breast cancer patients in a Phase II clinical trial of neoadjuvant chemotherapy and the expression pattern of growth factor receptor-binding protein 14 was determined by immunohistochemistry. Kaplan-Meier analysis and Cox regression model were used to assess disease-free and overall survival, according to the expression of growth factor receptor-binding protein 14 in tumor cells. RESULTS: Our result showed that growth factor receptor-binding protein 14 was highly expressed in 23.1% of breast cancer sections, and high expression of growth factor receptor-binding protein 14 was significantly associated with better disease-free (P = 0.016, hazard ratio 0.07, 95% confidence interval 0.06-0.08) and overall survival (P = 0.004, hazard ratio 0.02, 95% confidence interval 0.02-0.03), compared with the low-expression group. Multivariate analysis indicated that high expression of growth factor receptor-binding protein 14 was an independent good prognostic factor for both disease-free (P = 0.04, hazard ratio 0.37, 95% confidence interval 0.14-0.98) and overall survival (P = 0.03, hazard ratio 0.11, 95% confidence interval 0.10-0.82). CONCLUSIONS: High expression of growth factor receptor-binding protein 14 in breast cancer cells may help to identify low-risk patients for additional therapies after neoadjuvant chemotherapy.

[657]

TÍTULO / TITLE: - Combining Erlotinib and Cetuximab Is Associated with Activity in Patients with Non-Small Cell Lung Cancer (Including Squamous Cell Carcinomas) and Wild-Type EGFR or Resistant Mutations.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1208](#)

AUTORES / AUTHORS: - Wheler JJ; Tsimberidou AM; Falchook GS; Zinner RG; Hong DS; Fok JY; Fu S; Piha-Paul SA; Naing A; Kurzrock R

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Department of Investigational Cancer Therapeutics—a Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, Texas; and 2Moore's Cancer Center, University of California San Diego, La Jolla, California.

RESUMEN / SUMMARY: - Preclinical data suggest that combined EGF receptor (EGFR) targeting with an EGFR tyrosine kinase inhibitor and an anti-EGFR monoclonal antibody may be superior over single-agent targeting. Therefore, as part of a phase I study, we

analyzed the outcome of 20 patients with non-small cell lung cancer treated with the combination of erlotinib and cetuximab. EGFR mutation status was ascertained in a Clinical Laboratory Improvement Amendment-approved laboratory. There were 10 men; median number of prior therapies was five. Overall, two of 20 patients (10%) achieved partial response (PR), one of whom had a TKI-resistant EGFR insertion in exon 20, time to treatment failure (TTF) = 24+ months, and the other patient had squamous cell histology (EGFR wild-type), TTF = 7.4 months. In addition, three of 20 patients (15%) achieved stable disease (SD) \geq 6 six months (one of whom had wild-type EGFR and squamous cell histology, and two patients had an EGFR TKI-sensitive mutation, one of whom had failed prior erlotinib therapy). Combination therapy with erlotinib plus cetuximab was well tolerated. The most common toxicities were rash, diarrhea, and hypomagnesemia. The recommended phase II dose was erlotinib 150 mg oral daily and cetuximab 250 mg/m² i.v. weekly. In summary, erlotinib and cetuximab treatment was associated with SD \geq six months/PR in five of 20 patients with non-small cell lung cancer (25%), including individuals with squamous histology, TKI-resistant EGFR mutations, and wild-type EGFR, and those who had progressed on prior erlotinib after an initial response. This combination warrants further study in select populations of non-small cell lung cancer. Mol Cancer Ther; 12(10); 1-9. ©2013 AACR.

[658]

TÍTULO / TITLE: - High density of tryptase-positive mast cells in human colorectal cancer: a poor prognostic factor related to protease-activated receptor 2 expression.

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

REVISTA / JOURNAL: - J Cell Mol Med. 2013 Aug;17(8):1025-37. doi: 10.1111/jcmm.12073.

●● Enlace al texto completo (gratis o de pago) [1111/jcmm.12073](#)

AUTORES / AUTHORS: - Malfettone A; Silvestris N; Saponaro C; Ranieri G; Russo A; Caruso S; Popescu O; Simone G; Paradiso A; Mangia A

INSTITUCIÓN / INSTITUTION: - Functional Biomorphology Laboratory, National Cancer Research Centre "Giovanni Paolo II", Bari, Italy.

RESUMEN / SUMMARY: - Tryptase(+) mast cells (MCs), abundant in the invasive front of tumours, contribute to tissue remodelling. Indeed, protease-activated receptor-2 (PAR-2) activation by MC-tryptase is considered an oncogenic event in colorectal cancer (CRC). Recently, we have suggested NHERF1 as a potential new marker in CRC. In this study, we aimed to determine the distribution of tryptase(+) MCs and PAR-2 and to examine the relationship between PAR-2 and NHERF1, investigating their reputed usefulness as tumour markers. We studied a cohort of 115 CRC specimens including primary cancer © and adjacent normal mucosa (NM) by immunohistochemical double staining, analyzing the protein expression of MC-tryptase, PAR-2 and cytoplasmic NHERF1. MC density was higher in NM than in C.

Tumours with high TNM stage and poor grade showed the highest MC density. A higher PAR-2 immunoreactivity characterized tumours most infiltrated by MCs compared with samples with low MC density. Furthermore, PAR-2 overexpression was associated with advanced TNM stage, poor grade and lymphovascular invasion (LVI). A positive correlation existed between tryptase(+) MC density and PAR-2 expression. Cytoplasmic NHERF1 was higher in C than in NM and overexpressing tumours resulted associated with nodal and distant metastases, poor grade and LVI. PAR-2 correlated with cytoplasmic NHERF1 and the PAR-2(+)/cytoplasmic NHERF1(+) expression immunophenotype identified tumours associated with unfavourable prognosis and aggressive clinical parameters. Our data indicate that the high density of tryptase(+) MCs at invasive margins of tumours was associated with advanced stages of CRC and was strongly correlated with PAR-2 expression.

[659]

TÍTULO / TITLE: - Sulindac modulates secreted protein expression from LIM1215 colon carcinoma cells prior to apoptosis.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Nov;1834(11):2293-307. doi: 10.1016/j.bbapap.2013.07.007. Epub 2013 Jul 27.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbapap.2013.07.007](#)

AUTORES / AUTHORS: - Greening DW; Ji H; Kapp EA

INSTITUCIÓN / INSTITUTION: - La Trobe Institute for Molecular Science (LIMS), La Trobe University, Bundoora, Victoria, Australia.

RESUMEN / SUMMARY: - Colorectal cancer (CRC) is a major cause of mortality in Western populations. Growing evidence from human and rodent studies indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) cause regression of existing colon tumors and act as effective chemopreventive agents in sporadic colon tumor formation. Although much is known about the action of the NSAID sulindac, especially its role in inducing apoptosis, mechanisms underlying these effects is poorly understood. In previous secretome-based proteomic studies using 2D-DIGE/MS and cytokine arrays we identified over 150 proteins released from the CRC cell line LIM1215 whose expression levels were dysregulated by treatment with 1mM sulindac over 16h; many of these proteins are implicated in molecular and cellular functions such as cell proliferation, differentiation, adhesion, angiogenesis and apoptosis (Ji et al., Proteomics Clin. Appl. 2009, 3, 433-451). We have extended these studies and describe here an improved protein/peptide separation strategy that facilitated the identification of 987 proteins and peptides released from LIM1215 cells following 1mM sulindac treatment for 8h preceding the onset of apoptosis. This peptidome separation strategy involved fractional centrifugal ultrafiltration of concentrated cell culture media (CM) using nominal molecular weight membrane filters (NMWL 30K, 3K and 1K).

Proteins isolated in the >30K and 3-30K fractions were electrophoretically separated by SDS-PAGE and endogenous peptides in the 1-3K membrane filter were fractionated by RP-HPLC; isolated proteins and peptides were identified by nanoLC-MS-MS. Collectively, our data show that LIM1215 cells treated with 1mM sulindac for 8h secrete decreased levels of proteins associated with extracellular matrix remodeling (e.g., collagens, perlecan, syndecans, filamins, dyneins, metalloproteinases and endopeptidases), cell adhesion (e.g., cadherins, integrins, laminins) and mucosal maintenance (e.g., glycoprotein 340 and mucins 5AC, 6, and 13). A salient finding of this study was the increased proteolysis of cell surface proteins following treatment with sulindac for 8h (40% higher than from untreated LIM1215 cells); several of these endogenous peptides contained C-terminal amino acids from transmembrane domains indicative of regulated intramembrane proteolysis (RIP). Taken together these results indicate that during the early-stage onset of sulindac-induced apoptosis (evidenced by increased annexin V binding, dephosphorylation of focal adhesion kinase (FAK), and cleavage of caspase-3), 1mM sulindac treatment of LIM1215 cells results in decreased expression of secreted proteins implicated in ECM remodeling, mucosal maintenance and cell-cell-adhesion. This article is part of a Special Issue entitled: An Updated Secretome.

[660]

TÍTULO / TITLE: - Real-time nanoscale proteomic analysis of the novel multi-kinase pathway inhibitor rigosertib to measure the response to treatment of cancer.

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

REVISTA / JOURNAL: - Expert Opin Investig Drugs. 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago) [1517/13543784.2013.829453](#)

AUTORES / AUTHORS: - Fan AC; O'Rourke JJ; Praharaj DR; Felsher DW

INSTITUCIÓN / INSTITUTION: - Stanford University School of Medicine, Division of Oncology, Departments of Medicine and Pathology, Stanford, CA, USA
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RESUMEN / SUMMARY: - Introduction: Rigosertib (ON01910.Na), is a targeted therapeutic that inhibits multiple kinases, including PI3K and PIK-1. Rigosertib has been found to induce the proliferative arrest and apoptosis of myeloblasts but not of other normal hematopoietic cells. Rigosertib has significant clinical activity as a therapy for patients with high-risk myelodysplastic syndrome who are otherwise refractory to DNA methyltransferase inhibitors. Moreover, rigosertib has potential clinical activity in a multitude of solid tumors. Areas covered: The objective of this review is to evaluate the mechanism of activity, efficacy and dosing of rigosertib. Furthermore, the challenge in the clinical development of rigosertib, to identify the specific patients that are most likely to benefit from this therapeutic agent, is discussed. A PubMed search was performed using the following key words: rigosertib and ON01910.Na. Expert

opinion: We describe the application of a novel nanoscale proteomic assay, the nanoimmunoassay, a tractable approach for measuring the activity and predicting the efficacy of rigosertib, in real-time, using limited human clinical specimens. Our strategy suggests a possible paradigm where proteomic analysis during the pre-clinical and clinical development of a therapy can be used to uncover biomarkers for the analysis and prediction of efficacy in human patients.

TÍTULO / TITLE: - Gold nanoparticle delivery-enhanced proteasome inhibitor effect in adenocarcinoma cells.

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

REVISTA / JOURNAL: - Expert Opin Drug Deliv. 2013 Oct;10(10):1345-52. doi: 10.1517/17425247.2013.827659. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1517/17425247.2013.827659](https://doi.org/10.1517/17425247.2013.827659)

AUTORES / AUTHORS: - Coelho SC; Rocha S; Juzenas P; Sampaio P; Almeida GM; Silva FS; Pereira MC; Coelho MA

INSTITUCIÓN / INSTITUTION: - University of Porto, Faculty of Engineering, Department of Chemical Engineering, LEPAE, Rua Roberto Frias, PT-4200-465 Porto, Portugal +351 225081679; +351 225081449; mcoelho@fe.up.pt.

RESUMEN / SUMMARY: - Background: Proteasome inhibition is a current therapeutic strategy used in the treatment of multiple myeloma. Drugs controlling proteasome activity are ideally suited for unidirectional manipulation of cellular pathways such as apoptosis. The first proteasome inhibitor approved in clinics was bortezomib. This drug is currently used in combination with other anticancer agents. Objectives: In this study, the enhancement of bortezomib activity was evaluated using gold nanoparticles coated with poly(ethylene glycol). The uptake mechanism of the gold nanoparticles in pancreatic cell lines, S2-013 and hTERT-HPNE, was assessed by laser scanning confocal microscopy (LSCM). Results: Pancreatic cancer cells internalized the nanoparticles together with the drug in few minutes through the formation of endocytic vesicles. This rapid uptake leads to an increase in the concentration and diffusion of bortezomib in the cytoplasm yielding an increased toxicity on the cells when compared to the drug alone. Conclusion: Gold nanoparticles can be used as effective delivery systems to increasing the permeation and retention of drugs in cancer cells.

[661]

TÍTULO / TITLE: - The DNA methyl transferase inhibitor, 5'-aza-2-deoxycytidine, enhances the apoptotic effect of Mevastatin in human leukemia HL-60 cells.

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

REVISTA / JOURNAL: - Hum Exp Toxicol. 2013 Aug 5.

●● Enlace al texto completo (gratis o de pago) [1177/0960327113499050](https://doi.org/10.1177/0960327113499050)

AUTORES / AUTHORS: - Yilmaz A; Menevse S; Konac E; Alp E

INSTITUCIÓN / INSTITUTION: - 1Department of Medical Biology and Genetics, Faculty of Medicine, Gazi University, Besevler, Ankara, Turkey.

RESUMEN / SUMMARY: - Statins induce antiproliferative effects and apoptotic response in various cancer cell types. Moreover, they also sensitize tumor cell lines from different origins to many agents. We aimed to investigate possible effects of Mevastatin (Mev) alone and sequential treatment of 5'-aza-2-deoxycytidine (DAC) and Mev on HL-60 cell line using XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfohenyl)-2H-tetrazolium-5-carboxanilide) assay, lactate dehydrogenase release assay, fluorescence microscopy, DNA fragmentation analysis, determination of DNA synthesis rate, and active caspase-3 assay. Messenger RNA (mRNA) expression of apoptotic and antiapoptotic genes were also evaluated by semiquantitative reverse transcription-polymerase chain reaction (RT-PCR) for BAX, BCL2, and XIAP genes and quantitative Real-time PCR for CASP3, CASP8, and CASP9 genes. We showed that treatment with Mev alone and DAC followed by Mev resulted in apoptotic response in a time- and dose-dependent manner. We also found that pretreatment with DAC sensitized HL-60 cells to Mev and caused more apoptotic cell death than Mev-alone treatment via caspase-3 activation and DNA fragmentation. Moreover, sequential addition of Mev after DAC diminished DNA synthesis rate more effectively than Mev-alone treatment. Furthermore, DAC pretreatment significantly increased CASP3 and CASP9 mRNA expression even with lower doses of Mev. BAX, BCL2, and XIAP gene mRNA levels were also found to be changed in the presence of DAC and Mev. Determination of the exact molecular effects of statins and DAC would allow us to identify new molecular targets to develop more effective treatment regimens for cancer.

[662]

TÍTULO / TITLE: - Quantification of peripheral blood CD133 mRNA in identifying metastasis and in predicting recurrence of patients with clear cell renal cell carcinoma.

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

REVISTA / JOURNAL: - Urol Oncol. 2013 Sep 17. pii: S1078-1439(13)00252-4. doi: 10.1016/j.urolonc.2013.06.003.

●● Enlace al texto completo (gratis o de pago) 1016/j.urolonc.2013.06.003

AUTORES / AUTHORS: - Feng G; Jiang F; Pan C; Pu C; Huang H; Li G

INSTITUCIÓN / INSTITUTION: - Clinical Genetics Laboratory, Yijishan Hospital of Wannan Medical College, Wuhu, Anhui, China.

RESUMEN / SUMMARY: - OBJECTIVES: To investigate whether CD133 messenger ribonucleic acid (mRNA) could provide useful information to identify metastasis or predict recurrence in patients with clear cell renal cell carcinoma (cRCC). METHODS AND MATERIALS: This study included 86 patients with cRCC and 30 healthy controls. Real-time reverse transcriptase-polymerase chain reaction was used to quantify CD133 mRNA in peripheral blood mononuclear cells before nephrectomy. RESULTS: The

average CD133 mRNA in patients with metastatic cRCC (1.546+/-0.291) was significantly higher than that in those with localized cRCC (1.034+/-0.316, P = 0.022) or in controls (0.042+/-0.028, P = 0.001). Metastasis could be identified with a sensitivity of 82.6% at specificity of 69.8% by CD133 mRNA. Among patients with localized cRCC, there was a significant difference in CD133 mRNA between the patients with recurrence (1.136+/-0.127) and without recurrence (1.010+/-0.091, P = 0.047). Recurrence could be identified with a sensitivity of 75.0% at specificity of 61.8%. Patients with a higher CD133 mRNA had a significantly higher recurrence rate than those with a low CD133 mRNA (P = 0.019). CONCLUSIONS: CD133 mRNA can be useful for identifying metastasis, predicting recurrence, and stratifying the patients into different risk groups for possible adjuvant treatment.

[663]

TÍTULO / TITLE: - Anticancer effects of suberoylanilide hydroxamic acid in esophageal squamous cancer cells in vitro and in vivo.

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

REVISTA / JOURNAL: - Dis Esophagus. 2013 Sep 4. doi: 10.1111/dote.12127.

●● Enlace al texto completo (gratis o de pago) [1111/dote.12127](#)

AUTORES / AUTHORS: - Tzao C; Jin JS; Chen BH; Chung HY; Chang CC; Hsu TY; Sun GH

INSTITUCIÓN / INSTITUTION: - Division of Thoracic Surgery, Tri-Service General Hospital, Taichung, Taiwan; Department and Graduate Institute of Microbiology and Immunology, National Defense Medical Center, Taichung, Taiwan.

RESUMEN / SUMMARY: - The effects of suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, have not been studied in esophageal squamous cell cancer (ESCC). Cell viability assay; flow cytometry for cell cycle and annexin V apoptosis assays; assays for cell migration, invasion, and adhesion to extracellular matrix (ECM); and immunoblotting and immunofluorescence staining were performed in three ESCC cell lines. Tumor xenograft with semiquantitative immunohistochemistry was used to study the effects of SAHA in vivo. SAHA effectively inhibited growth of ESCC cells with half-inhibitory concentrations (IC50) ranging from 2.6 to 6.5 $\mu\text{mol/L}$. SAHA restored acetylation of histone 3 lysine 9 (H3K9Ac) and histone 4 lysine 12 (H4K12Ac) with an induction of G1 or G2 cell cycle arrest and apoptosis. Expression of cell cycle checkpoint regulatory proteins including cyclin-dependent kinases (CDKs) and cyclins was decreased, whereas expression of cell cycle suppressors, p21, p27, and Rb was increased in ESCC cells after SAHA treatment. SAHA inhibited migration, invasion, and ECM adhesion in ESCC cells with an induction of E-cadherin expression. SAHA significantly inhibited growth of ESCC tumors with increased expression of p21, p27, Rb, and E-cadherin while decreasing expression of CDK4 and cyclin D1 within the murine tumors. In conclusion, SAHA had antigrowth activity against ESCC cells in vitro

and in vivo while inhibiting cell migration, cell invasion, and ECM adhesion, suggesting its potential as an epigenetic therapeutic agent for ESCC.

[664]

TÍTULO / TITLE: - Xbp1s-negative tumor B cells and pre-plasmablasts mediate therapeutic proteasome inhibitor resistance in multiple myeloma.

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

REVISTA / JOURNAL: - Cancer Cell. 2013 Sep 9;24(3):289-304. doi: 10.1016/j.ccr.2013.08.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.ccr.2013.08.009](#)

AUTORES / AUTHORS: - Leung-Hagesteijn C; Erdmann N; Cheung G; Keats JJ; Stewart AK; Reece DE; Chung KC; Tiedemann RE

INSTITUCIÓN / INSTITUTION: - Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada.

RESUMEN / SUMMARY: - Proteasome inhibitor (PI) resistance mechanisms in multiple myeloma (MM) remain controversial. We report the existence of a progenitor organization in primary MM that recapitulates maturation stages between B cells and plasma cells and that contributes to clinical PI resistance. Xbp1s(-) tumor B cells and pre-plasmablasts survive therapeutic PI, preventing cure, while maturation arrest of MM before the plasmablast stage enables progressive disease on PI treatment. Mechanistically, suppression of Xbp1s in MM is shown to induce bortezomib resistance via de-commitment to plasma cell maturation and immunoglobulin production, diminishing endoplasmic reticulum (ER) front-loading and cytotoxic susceptibility to PI-induced inhibition of ER-associated degradation. These results reveal the tumor progenitor structure in MM and highlight its role in therapeutic failure.

[665]

TÍTULO / TITLE: - Galectin-3 inhibition sensitizes human renal cell carcinoma cells to arsenic trioxide treatment.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 5;14(10).

AUTORES / AUTHORS: - Xu Y; Gu X; Gong M; Guo G; Han K; An R

INSTITUCIÓN / INSTITUTION: - Department of Urological Surgery; The Affiliated Tumor Hospital of Harbin Medical University; Heilongjian, PR China.

RESUMEN / SUMMARY: - The anti-tumor effects of arsenic trioxide (ATO) were well established in acute promyelocytic leukemia, but not in renal cell carcinoma (RCC). Recent evidences indicate that Galectin-3 (Gal-3) plays an anti-apoptotic role in chemotherapy induced tumor cell death. This study was intended to clarify the exact roles of Gal-3 performed in ATO-induced apoptosis in RCC cells. Weak apoptosis was

observed in Gal-3-positive RCC cells (Caki-1, Caki-2, 786-0, and ACHN) following ATO treatment. However, ATO treatment upregulated Gal-3 expression concurrently caused a Synexin-cooperated translocation of Gal-3 from the nucleus to the cytoplasm. Gal-3-knockdown cells were more sensitive to ATO treatment as indicated by a strong mitochondria-dependent apoptosis following ATO treatment. Meanwhile, Gal-3 was found to inhibit ATO-induced apoptosis through enhancing Bcl-2 expression and stabilizing mitochondria. To confirm the results obtained from genetic method, we employed a Gal-3 inhibitor, modified citrus pectin (MCP), and co-treated the RCC cells with ATO. The cells showed an increased apoptosis in the syngeneic application of Gal-3 inhibition and ATO compared with ATO application alone. Based on these results, we conclude that Gal-3 inhibition sensitizes human renal cell carcinoma cells to ATO treatment through increasing mitochondria-dependent apoptosis. Our studies implicate synergetic application of ATO and Gal-3 inhibition as a potential strategy for RCC treatment.

[666]

TÍTULO / TITLE: - Long-term efficacy of low-dose all-trans retinoic acid plus minimal chemotherapy induction followed by the addition of intravenous arsenic trioxide post-remission therapy in newly diagnosed acute promyelocytic leukaemia.

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

REVISTA / JOURNAL: - Hematol Oncol. 2013 Aug 20. doi: 10.1002/hon.2076.

●● [Enlace al texto completo \(gratis o de pago\) 1002/hon.2076](#)

AUTORES / AUTHORS: - Lou Y; Qian W; Meng H; Mai W; Tong H; Tong Y; Huang J; Jin J

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Institute of Hematology, The First Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, Zhejiang Province, China.

RESUMEN / SUMMARY: - We evaluated the efficacy of low-dose all-trans retinoic acid (ATRA) plus minimal chemotherapy for induction in newly diagnosed acute promyelocytic leukaemia (APL). Furthermore, we compared its long-term outcome with or without the addition of intravenous arsenic trioxide (ATO) in post-remission therapy. From January 2004 to September 2011, a total of 109 patients with a median age of 41 years (range 14-73) were enrolled in the study. Two arms were assigned according to post-remission protocols: ATO group cases were subsequently treated with intravenous ATO, standard chemotherapy, and ATRA. No-ATO group cases were subsequently treated with chemotherapy and ATRA only. Patients were monitored of minimal residual disease (MRD) by reverse-transcriptase polymerase chain reaction. The haematologic complete remission (CR) rate was 96.3%. The early death rate was 0.9%. At a median follow-up of 49 months (range 8-102 months), the Kaplan-Meier estimates of 5-year relapse-free survival were significantly better for patients in the ATO group than in the no-ATO group, 94.4% vs 54.8% ($p = 0.0001$), and the 5-year

overall survival rate was 95.7% vs 64.1%, in the two groups ($p = 0.003$). Our data show that low-dose ATRA plus minimal chemotherapy exhibits efficacy in induction therapy for untreated APL and suggest that the addition of ATO to post-remission therapy significantly improves the long-term outcome. Copyright © 2013 John Wiley & Sons, Ltd.

[667]

TÍTULO / TITLE: - Discovery of 4-amino-2-(thio)phenol derivatives as novel protein kinase and angiogenesis inhibitors for the treatment of cancer: Synthesis and biological evaluation. Part II.

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

REVISTA / JOURNAL: - Eur J Med Chem. 2013 Aug 29;69C:191-200. doi: 10.1016/j.ejmech.2013.07.056.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.07.056](http://dx.doi.org/10.1016/j.ejmech.2013.07.056)

AUTORES / AUTHORS: - Xu F; Zhang L; Jia Y; Wang X; Li X; Wen Q; Zhang Y; Xu W

INSTITUCIÓN / INSTITUTION: - Department of Medicinal Chemistry, School of Pharmacy, Shandong University, Ji'nan, Shandong 250012, PR China.

RESUMEN / SUMMARY: - A novel series of 4-amino-2-(thio)phenol derivatives were well synthesized. The preliminary biological test revealed that several compounds displayed high specific protein kinase and angiogenesis inhibitory activities compared with previous work mainly because of the substitution of sulfonamide structure for amide fragment. Among which, compound 5i was identified to inhibit protein kinase B/AKT ($IC_{50} = 1.26 \mu M$) and ABL tyrosine kinase ($IC_{50} = 1.50 \mu M$) effectively. Meanwhile, compound 5i demonstrated competitive in vitro antiangiogenic activities to Pazopanib in both human umbilical vein endothelial cell (HUVEC) tube formation assay and the rat thoracic aorta rings test.

[668]

TÍTULO / TITLE: - Prognostic value of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 blood levels in breast cancer.

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

REVISTA / JOURNAL: - Breast. 2013 Aug 19. pii: S0960-9776(13)00203-8. doi: 10.1016/j.breast.2013.07.038.

●● Enlace al texto completo (gratis o de pago) [1016/j.breast.2013.07.038](http://dx.doi.org/10.1016/j.breast.2013.07.038)

AUTORES / AUTHORS: - Hartog H; Boezen HM; de Jong MM; Schaapveld M; Wesseling J; van der Graaf WT

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Electronic address: hermienhartog@hotmail.com.

RESUMEN / SUMMARY: - High circulating insulin-like growth factor 1 (IGF-1) levels are firmly established as a risk factor for developing breast cancer, especially estrogen positive tumors. The effect of circulating IGF-1 on prognosis once a tumor is established is unknown. The authors explored the effect of IGF-1 blood levels and of its main binding protein, IGFBP-3, on overall survival and occurrence of second primary breast tumors in breast cancer patients, as well as reproductive and lifestyle factors that could modify this risk. Patients were accrued from six hospitals in the Netherlands between 1998 and 2003. Total IGF-1 and IGFBP-3 were measured in 582 plasma samples. No significant association between IGF-1 and IGFBP-3 plasma levels and overall survival was found. However, in a multivariate Cox regression model including standard prognostic variables high IGF-1 levels were related to worse overall survival in patients receiving endocrine therapy (HR = 1.37, 95% CI: 1.11, 1.69, P 0.004). These data at least indicate that higher IGF-1 levels, and as a consequence most likely IGF-1-induced signaling, are related to a less favorable overall survival in breast cancer patients treated with endocrine therapy. Interventions aimed at reducing circulating levels of IGF-1 in hormone receptor positive breast cancer may improve survival.

[669]

TÍTULO / TITLE: - Fenretinide targets chronic myeloid leukemia stem/progenitor cells by regulation of redox signaling.

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

REVISTA / JOURNAL: - Antioxid Redox Signal. 2013 Sep 11.

●● Enlace al texto completo (gratis o de pago) [1089/ars.2012.4935](#)

AUTORES / AUTHORS: - Du Y; Xia Y; Pan X; Chen Z; Wang A; Wang K; Li J; Zhang J

INSTITUCIÓN / INSTITUTION: - Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS), Shanghai, China ; yzdu@sibs.ac.cn.

RESUMEN / SUMMARY: - Aims: We have recently shown that fenretinide preferentially targets CD34+ cells of acute myeloid leukemia (AML), and here we test whether this agent exerts the effect on CD34+ cells of chronic myeloid leukemia (CML), which are refractory to imatinib. Results: As tested by colony forming cell assays using clinical specimens, both number and size of total colonies derived from CD34+ CML cells were significantly reduced by fenretinide, and by combining fenretinide with imatinib. In particular, colonies derived from erythroid progenitors and more primitive pluripotent/multipotent progenitors were highly sensitive to fenretinide/fenretinide plus imatinib. Accordingly, fenretinide appeared to induce apoptosis in CD34+ CML cells, particularly with respect to the cells in the subpopulation of CD34+CD38-. Through cell quiescent assays including Ki-67 negativity test, we added evidence that non-proliferative CD34+ CML cells were largely eliminated by fenretinide.

Transcriptome and molecular data further showed that mechanisms underlying the apoptosis in CD34+ CML cells were highly complex, involving multiple events of oxidative stress responses. Innovation and Conclusion: As compared to CD34+ AML cells, the apoptotic effects of fenretinide on CD34+ CML cells were more prominent whereas less varied among the samples of different patients, and also various stress responsive events appeared to be more robust in fenretinide treated CD34+ CML cells. Thus, the combination of fenretinide with imatinib may represent a more sophisticated strategy for CML treatment, in which imatinib mainly targets leukemic blast cells through the intrinsic pathway of apoptosis, whereas fenretinide primarily targets CML stem/progenitor cells through the oxidative/endoplasmic reticulum stress-mediated pathway.

[670]

TÍTULO / TITLE: - Novel sorafenib analogues induce apoptosis through SHP-1 dependent STAT3 inactivation in human breast cancer cells.

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

REVISTA / JOURNAL: - Breast Cancer Res. 2013 Aug 12;15(4):R63.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3457](#)

AUTORES / AUTHORS: - Liu CY; Tseng LM; Su JC; Chang KC; Chu PY; Tai WT; Shiao CW; Chen KF

INSTITUCIÓN / INSTITUTION: - Institute of Biopharmaceutical Sciences, National Yang-Ming University, No, 155 Sec, 2, Li-Nong Street, Taipei 112, Taiwan.

cwshiau@ym.edu.tw.

RESUMEN / SUMMARY: - INTRODUCTION: Signal transducers and activators of transcription 3 (STAT3) signaling is constitutively activated in various cancers including breast cancer and has emerged as a novel potential anti-cancer target. STAT3 has been demonstrated to be a target of sorafenib, and a protein tyrosine phosphatase Src homology 2-domain containing tyrosine phosphatase 1 (SHP-1) has been demonstrated to downregulate p-STAT3 via its phosphatase activity. Here, we tested the efficacy of two sorafenib analogues, SC-1 and SC-43, in breast cancer cells and examined the drug mechanism. METHODS: Breast cancer cell lines were used for in vitro studies. Cell viability was examined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Apoptosis was examined by flow cytometry and western blot. Signal transduction pathways in cells were assessed by western blot. In vivo efficacy of sorafenib, SC-1 and SC-43 was tested in xenografted nude mice. RESULTS: SC-1 and SC-43 induced more potent apoptosis than sorafenib, in association with downregulation of p-STAT3 and its downstream proteins cyclin D1 and survivin in a dose-dependent manner in breast cancer cell lines (HCC-1937, MDA-MB-468, MDA-MB-231, MDA-MB-453, SK-BR3, MCF-7). Overexpression of STAT3 in MDA-MB-468 cells protected the cells from apoptosis induced by sorafenib, SC-1 and SC-43.

Moreover, SC-1 and SC-43 upregulated SHP-1 activity to a greater extent than sorafenib as measured by in vitro phosphatase assays. Knockdown of SHP-1 by siRNA reduced apoptosis induced by SC-1 and SC-43. Importantly, SC-1 and SC-43 showed more efficacious antitumor activity and p-STAT3 downregulation than sorafenib in MDA-MB-468 xenograft tumors. CONCLUSIONS: Novel sorafenib analogues SC-1 and SC-43 induce apoptosis through SHP-1 dependent STAT3 inactivation and demonstrate greater potency than sorafenib in human breast cancer cells.

[671]

TÍTULO / TITLE: - Selective cytotoxicity, inhibition of cell cycle progression, and induction of apoptosis in human breast cancer cells by sesquiterpenoids from *Inula lineariifolia* Turcz.

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

REVISTA / JOURNAL: - Eur J Med Chem. 2013 Aug 11;68C:473-481. doi: 10.1016/j.ejmech.2013.07.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.07.018](https://doi.org/10.1016/j.ejmech.2013.07.018)

AUTORES / AUTHORS: - Qin JJ; Jin HZ; Huang Y; Zhang SD; Shan L; Voruganti S; Nag S; Wang W; Zhang WD; Zhang R

INSTITUCIÓN / INSTITUTION: - School of Pharmacy, Shanghai Jiao Tong University, Shanghai 200240, PR China; Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, TX 79106, USA.

RESUMEN / SUMMARY: - Four new sesquiterpenoid dimers (lineariifolianoids E-H, 1-4), five new sesquiterpenoids (5-9), and seven known sesquiterpenoids (10-16) were isolated from the aerial parts of *Inula lineariifolia* Turcz. Their structures were determined by spectroscopic data analysis and X-ray diffraction studies. The compounds were then evaluated for their in vitro cytotoxicity against two human breast cancer cell lines (MCF-7 and MDA-MB-231) and one normal breast cell line (MCF-10^a). Lineariifolianoid E (1) showed IC₅₀ values of 1.56 μM and 2.75 μM against MCF-7 and MDA-MB-231, respectively. However, lineariifolianoid E demonstrated low toxicity to MCF-10^a cells, which indicated a selective cytotoxicity for tumor cells. Further studies also presented that lineariifolianoid E had significant, dose-dependent effects on cell cycle progression and apoptosis in breast cancer cells.

[672]

TÍTULO / TITLE: - Interplay between autophagy and apoptosis mediated by copper oxide nanoparticles in human breast cancer cells MCF7.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 17. pii: S0304-4165(13)00355-3. doi: 10.1016/j.bbagen.2013.08.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbagen.2013.08.011](https://doi.org/10.1016/j.bbagen.2013.08.011)

AUTORES / AUTHORS: - Laha D; Pramanik A; Maity J; Mukherjee A; Pramanik P; Laskar A; Karmakar P

INSTITUCIÓN / INSTITUTION: - Department of Life Science and Biotechnology, Jadavpur University, Kolkata, 700 032, India.

RESUMEN / SUMMARY: - BACKGROUND: Metal oxide nanoparticles are well known to generate oxidative stress and deregulate normal cellular activities. Among these, transition metals copper oxide nanoparticles (CuO NPs) are more compelling than others and able to modulate different cellular responses. METHODS: In this work, we have synthesized and characterized CuO NPs by various biophysical methods. These CuO NPs (~30nm) induce autophagy in human breast cancer cell line, MCF7 in a time- and dose-dependent manner. Cellular autophagy was tested by MDC staining, induction of green fluorescent protein-light chain 3 (GFP-LC3B) foci by confocal microscopy, transfection of pBABE-puro mCherry-EGFP-LC3B plasmid and Western blotting of autophagy marker proteins LC3B, beclin1 and ATG5. Further, inhibition of autophagy by 3-MA decreased LD50 doses of CuO NPs. Such cell death was associated with the induction of apoptosis as revealed by FACS analysis, cleavage of PARP, dephosphorylation of Bad and increased cleavage product of caspase 3. siRNA mediated inhibition of autophagy related gene beclin1 also demonstrated similar results. Finally induction of apoptosis by 3-MA in CuO NP treated cells was observed by TEM. RESULTS: This study indicates that CuO NPs are a potent inducer of autophagy which may be a cellular defense against the CuO NP mediated toxicity and inhibition of autophagy switches the cellular response into apoptosis. CONCLUSIONS: A combination of CuO NPs with the autophagy inhibitor is essential to induce apoptosis in breast cancer cells. GENERAL SIGNIFICANCE: CuO NP induced autophagy is a survival strategy of MCF7 cells and inhibition of autophagy renders cellular fate to apoptosis.

[673]

TÍTULO / TITLE: - Evaluation of Expression of the PTEN Gene, Oestrogen and Progesterone Receptors as Diagnostic and Predictive Factors in Endometrial Cancer.

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

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Sep 13.

●● Enlace al texto completo (gratis o de pago) [1007/s12253-013-9684-3](https://doi.org/10.1007/s12253-013-9684-3)

AUTORES / AUTHORS: - Samulak D; Grosman-Dziewiszek P; Michalska MM; Mojs E; Samulak K; Romanowicz H; Smolarz B

INSTITUCIÓN / INSTITUTION: - Cathedral of Mother's and Child's Health, Poznan University of Medical Sciences, ul. Polna 33, 60-535, Poznan, Poland.

RESUMEN / SUMMARY: - Endometrial cancer belongs to the commonest malignancy in females after breast cancer, malignant neoplasm of female genitals in Europe and North America but there is still not significant improvement as far as the curability of

this neoplasm is concerned, especially its advanced forms. That is why there is need to define new factors that could be not only diagnostic but also predictive factors. In present study we analyzed the mRNA PTEN expression by quantitative real-time polymerase chain reaction (Q-PCR) in 123 women of endometrial carcinoma and 14 women of control group. Moreover we assessed oestrogen (ER) and progesterone receptors (PgR) in all cases. We defined the correlation between expression of PTEN gene and receptors and between PTEN expression and maturity grade of cancer. Neoplasm advancement grade G1 was diagnosed in 82.11 % of patients (n = 101), G2 in 9.76 % of patients (n = 12) and G3 in 8.13 % of patients (n = 10). Presence of ER and PgR and decreased expression of PTEN gene was found in majority of patients with endometrial cancer (79.12 % and 59.34 % respectively) and the most numerous group was with weak expression of ER and strong expression of PgR. There was no statistically significant difference in gene expression depending on receptors expression nor maturity grade of cancer ($p > 0.05$). Evaluation of expression of PTEN gene may turn out to be a very useful tool aimed at qualifying patients for different therapies of endometrial cancer and at searching of new diagnostic and therapeutic methods of this cancer independently on its receptor status nor maturity grade of cancer.

[674]

TÍTULO / TITLE: - Phase II Trial of Erlotinib Plus Gemcitabine Chemotherapy in Korean Patients with Advanced Pancreatic Cancer and Prognostic Factors for Chemotherapeutic Response.

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

REVISTA / JOURNAL: - Gut Liver. 2013 Sep;7(5):611-5. doi: 10.5009/gnl.2013.7.5.611. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [5009/gnl.2013.7.5.611](#)

AUTORES / AUTHORS: - Park S; Chung MJ; Park JY; Chung JB; Bang S; Park SW; Song SY

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Graduate School, Yonsei University College of Medicine, Seoul, Korea. ; Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND/AIMS: Erlotinib and gemcitabine combined chemotherapy is becoming the treatment of choice in advanced pancreatic cancer. We evaluated the effectiveness of treatment with erlotinib plus gemcitabine and the prognostic factors for chemotherapeutic response in Korean pancreatic cancer patients. METHODS: Sixty-nine patients with advanced pancreatic cancer who were treated with daily erlotinib 100 mg orally and gemcitabine 1,000 mg/m²/30 min intravenous infusion on days 1, 8, and 15 of each 4-week cycle from 2006 to 2009 were included in this study. This study was a phase II single-center trial. RESULTS: All 69 patients with advanced pancreatic cancer were chemotherapy-naive. The objective

response rate was 18.8%, and the overall tumor-stabilization rate was 49.2%. The median overall survival was 7.7 months (95% confidence interval [CI], 6.0 to 9.4 months). The median progression-free survival was 1.9 months (95% CI, 1.4 to 2.5 months). Prognostic factors for good chemotherapeutic response were good performance status and the presence of skin rash during chemotherapy. Patients with lower performance scores showed worse chemotherapeutic responses (odds ratio [OR], 7.6; 95% CI, 2.4 to 24.8). Poor responses were predicted by the absence of skin rash during chemotherapy (OR, 3.0; 95% CI, 1.4 to 6.3). CONCLUSIONS: Erlotinib and gemcitabine chemotherapy is a tolerable treatment regimen and has a favorable therapeutic effect in Korean patients with advanced pancreatic cancer.

[675]

TÍTULO / TITLE: - Correlation of human epidermal growth factor receptor 2 (HER-2/neu) receptor status with hormone receptors Oestrogen Receptor, Progesterone Receptor status and other prognostic markers in breast cancer: an experience at tertiary care hospital in Karachi.

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

REVISTA / JOURNAL: - J Pak Med Assoc. 2013 Jul;63(7):854-8.

AUTORES / AUTHORS: - Mujtaba S; Haroon S; Faridi N; Lodhi FR

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Liaquat National Hospital, The Aga Khan University, Karachi.

RESUMEN / SUMMARY: - OBJECTIVE: To determine the frequency of human epidermal growth factor receptor 2 (HER-2/neu) positivity and to correlate its status in breast cancer patients with other prognostic markers. METHODS: The comparative cross-sectional study was conducted at the Department of Histopathology, Liaquat National Hospital, Karachi, from January 1 to October 31, 2010. It included all specimens of mastectomy and lumpectomy with axillary tissue. Incisional, trucut and wedge biopsies as well as all non-epithelial tumours were excluded. All samples were processed as per standard guidelines and were evaluated by immunohistochemistry. SPSS 10 was used for statistical analysis. RESULTS: The age of the 100 cases in the study ranged from 20 to 82 years with a mean of 51+/-17.6 years. Two (2%) of the patients were males. HER-2/neu over-expression increased with increasing tumour size, grade, lymph node metastasis and with oestrogen receptor and progesterone receptor negativity. No significant correlation of HER-2/neu was seen with the age of patient and with the tumour type. CONCLUSIONS: The expression of HER-2/neu was associated with decrease in oestrogen receptor and progesterone receptor positivity, and increase in tumour size, high tumour grade and lymph node metastasis.

[676]

TÍTULO / TITLE: - Axl mediates acquired resistance of head and neck cancer cells to the epidermal growth factor receptor inhibitor erlotinib.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 11.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0170](#)

AUTORES / AUTHORS: - Giles KM; Kalinowski FC; Candy PA; Epis MR; Zhang PM; Redfern AD; Stuart LM; Goodall GJ; Leedman PJ

INSTITUCIÓN / INSTITUTION: - 1Laboratory for Cancer Medicine, Western Australian Institute for Medical Research.

RESUMEN / SUMMARY: - Elevated expression and activity of the epidermal growth factor receptor (EGFR) is associated with development and progression of head and neck cancer (HNC) and a poor prognosis. Clinical trials with EGFR tyrosine kinase inhibitors (TKIs; eg. erlotinib) have been disappointing in HNC. To investigate the mechanisms mediating resistance to these agents, we developed a HNC cell line (HN5-ER) with acquired erlotinib resistance. In contrast to parental HN5 HNC cells, HN5-ER cells exhibited an epithelial-mesenchymal (EMT) phenotype with increased migratory potential, reduced E-cadherin and epithelial-associated miRNAs, and elevated vimentin expression. Phosphorylated RTK profiling identified Axl activation in HN5-ER cells. Growth and migration of HN5-ER cells was blocked with a specific Axl inhibitor, R428, and R428 re-sensitized HN5-ER cells to erlotinib. Microarray analysis of HN5-ER cells confirmed the EMT phenotype associated with acquired erlotinib resistance, and identified activation of gene expression associated with cell migration and inflammation pathways. Moreover, increased expression and secretion of interleukin (IL)-6 and IL-8 in HN5-ER cells suggested a role for inflammatory cytokine signaling in EMT and erlotinib resistance. Expression of the tumor suppressor miR-34^a was reduced in HN5-ER cells and increasing its expression abrogated Axl expression and reversed erlotinib resistance. Finally, analysis of 302 HNC patients revealed that high tumor Axl mRNA expression was associated with poorer survival (HR 1.66, p=0.007). In summary, our results identify Axl as a key mediator of acquired erlotinib resistance in HNC and suggest that therapeutic inhibition of Axl by small molecule drugs or specific miRNAs might overcome anti-EGFR therapy resistance.

[677]

TÍTULO / TITLE: - Rare and complex mutations of epidermal growth factor receptor, and efficacy of tyrosine kinase inhibitor in patients with non-small cell lung cancer.

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

REVISTA / JOURNAL: - Int J Clin Oncol. 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1007/s10147-013-0602-1](#)

AUTORES / AUTHORS: - Keam B; Kim DW; Park JH; Lee JO; Kim TM; Lee SH; Chung DH; Heo DS

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

RESUMEN / SUMMARY: - BACKGROUND: There are many complex and rare mutations in the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) other than the two classical mutations of L858R and exon 19 deletional mutation. The purpose of this study was to investigate the clinical significance of rare and complex mutations, and the efficacy of EGFR tyrosine kinase inhibitors (TKIs). METHODS: We analyzed 1,431 NSCLC patients who were treated with either gefitinib or erlotinib. Exons 18 to 21 of EGFR were analyzed by PCR and subjected to direct sequencing methods. RESULTS: Of 306 patients who had EGFR mutation, 24 patients (7.3 %) had complex mutations. The frequency of rare mutations was 10.3 %. Four groups were categorized [group A (N = 269): classical mutation alone; group B (N = 16): complex mutation with classical mutation; group C (N = 16): rare mutation alone or complex mutation with rare mutation; group D (N = 5): classical mutation with T790M]; the response rate (RR) to TKI was significantly different between each group (RR = 74.8 % in group A vs. 68.8 % in group B vs. 25.0 % in group C vs. 80.0 % in group D, $P < 0.001$). Progression-free survival (PFS) was also poorer in rare mutations (median PFS: 11.9 vs. 8.1 vs. 1.4 vs. 8.0 months, respectively, $P < 0.001$). CONCLUSIONS: NSCLC patients harboring rare mutations did not show consistent and favorable responses to EGFR TKI compared with those harboring classical mutations. However, complex mutations with classical mutations showed similar treatment efficacy toward EGFR TKI to that with classical mutations alone.

[678]

TÍTULO / TITLE: - DNA Damage Response-Related Proteins in Gastric Cancer: ATM, Chk2 and p53 Expression and Their Prognostic Value.

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

REVISTA / JOURNAL: - Pathobiology. 2013 Aug 21;81(1):25-35.

- [Enlace al texto completo \(gratis o de pago\) 1159/000351072](#)

AUTORES / AUTHORS: - Lee HE; Han N; Kim MA; Lee HS; Yang HK; Lee BL; Kim WH
INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University Hospital, Seoul, South Korea.

RESUMEN / SUMMARY: - Objectives: The aims of this study were to assess expressions of the DNA damage response (DDR)-related proteins and to investigate their clinical significances in gastric carcinoma. Methods: Two independent cohorts, a training set (n = 524) and validation set (n = 394), of gastric cancer patients were enrolled. Ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (Chk2), and p53 expressions were examined by immunohistochemistry using tissue microarray. Results: ATM loss, Chk2

loss, and p53 positivity were observed in 21.8, 14.1, and 36.1% of the training set, and in 17.3, 12.2, and 35.8% of the validation set, respectively. In the training set, the aberrant expressions of ATM, Chk2, or p53 were significantly associated with an advanced TNM stage and poor disease-specific survival. This association was verified in the validation set. Chk2 positivity and p53 negativity were significantly related to a prolonged disease-specific survival. Also, patients with nonaberrant expressional levels of all 3 DDR-related proteins had a more favorable outcome than others. Multivariate analyses showed that Chk2 loss and at least 1 aberrant DDR-related protein remained as independent prognostic factors of poor disease-specific survival. Conclusions: This study elucidated the prognostic implications of DDR-related proteins, and suggests that their aberrant expressions play critical roles in the development and progression of gastric cancer.

[679]

TÍTULO / TITLE: - Differential Induction of Apoptosis and Senescence by the DNA Methyltransferase Inhibitors 5-Azacytidine and 5-Aza-2'-Deoxycytidine in Solid Tumor Cells.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-](#)

[0137](#)

AUTORES / AUTHORS: - Venturelli S; Berger A; Weiland T; Essmann F; Waibel M; Nuebling T; Hacker S; Schenk M; Schulze-Osthoff K; Salih HR; Fulda S; Sipos B; Johnstone RW; Lauer UM; Bitzer M

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Department of Gastroenterology and Hepatology, Medical University Hospital; 2Interfaculty Institute for Biochemistry, University of Tuebingen; 3Department of Hematology and Oncology, Eberhard Karls University; Departments of 4General, Visceral, and Transplant Surgery, and 5Pathology, University Hospital Tuebingen, Tuebingen; 6German Cancer Consortium (DKTK) and German Cancer Research Center, Heidelberg; 7University Children's Hospital, Ulm University, Ulm; and 8Institute for Experimental Cancer Research in Pediatrics, Goethe University Frankfurt, Frankfurt, Germany; and 9Cancer Immunology Program, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia.

RESUMEN / SUMMARY: - Epigenetic alterations are a hallmark of cancer that govern the silencing of genes. Up to now, 5-azacytidine (5-aza-CR, Vidaza) and 5-aza-2'-deoxycytidine (5-aza-dC, Dacogen) are the only clinically approved DNA methyltransferase inhibitors (DNMTi). Current effort tries to exploit DNMTi application beyond acute leukemia or myelodysplastic syndrome, especially to solid tumors. Although both drugs only differ by a minimal structural difference, they trigger distinct molecular mechanisms that are highly relevant for a rational choice of new

combination therapies. Therefore, we investigated cell death pathways in vitro in human hepatoma, colon, renal, and lung cancer cells and in vivo in chorioallantoic membrane and xenograft models. Real-time cancer cell monitoring and cytokine profiling revealed a profoundly distinct response pattern to both drugs. 5-aza-dC induced p53-dependent tumor cell senescence and a high number of DNA double-strand breaks. In contrast, 5-aza-CR downregulated p53, induced caspase activation and apoptosis. These individual response patterns of tumor cells could be verified in vivo in chorioallantoic membrane assays and in a hepatoma xenograft model. Although 5-aza-CR and 5-aza-dC are viewed as drugs with similar therapeutic activity, they induce a diverse molecular response in tumor cells. These findings together with other reported differences enable and facilitate a rational design of new combination strategies to further exploit the epigenetic mode of action of these two drugs in different areas of clinical oncology. Mol Cancer Ther; 12(10); 1-11. ©2013 AACR.

[680]

TÍTULO / TITLE: - AMG 900, a small molecule inhibitor of aurora kinases, potentiates the activity of microtubule-targeting agents in human metastatic breast cancer models.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Aug 29.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1178](#)

AUTORES / AUTHORS: - Bush TL; Payton M; Heller S; Chung G; Hanestad K; Rottman JB; Loberg R; Friberg G; Kendall RL; Saffran D; Radinsky R

INSTITUCIÓN / INSTITUTION: - 1Therapeutic Innovation Unit, Amgen Inc.

RESUMEN / SUMMARY: - Breast cancer is the most prevalent malignancy affecting women and ranks second in cancer deaths, where death occurs primarily from metastatic disease. Triple-negative breast cancer (TNBC) is a more aggressive and metastatic subtype of breast cancer that is initially responsive to treatment of microtubule-targeting agents (MTAs) such as taxanes. Recently, we reported the characterization of AMG 900, an orally bioavailable, potent and highly selective pan-aurora kinase inhibitor that is active in multidrug resistant cell lines. In this report, we investigate the activity of AMG 900 alone and in combination with two distinct classes of MTAs (taxanes and epothilones), in multidrug resistant TNBC cell lines and xenografts. In TNBC cells, AMG 900 inhibited phosphorylation of histone H3 on Ser10, a proximal substrate of aurora-B, and induced polyploidy and apoptosis. Furthermore, AMG 900 potentiated the antiproliferative effects of paclitaxel and ixabepilone at low nanomolar concentrations. In mice, AMG 900 significantly inhibited the growth of MDA-MB-231 (F11) (parental), MDA-MB-231 (F11) PTX-r (paclitaxel resistant variant), and DU4475 xenografts. The combination of AMG 900 with docetaxel enhanced tumor inhibition in MDA-MB-231 (F11) xenografts compared with either monotherapy.

Notably, combining AMG 900 with ixabepilone resulted in regressions of MDA-MB-231 (F11) PTX-r xenografts, in which >50% of the tumors failed to regrow 75 days after the cessation of drug treatment. These findings suggest that AMG 900, alone and in combination with MTAs, may be an effective intervention strategy for the treatment of metastatic breast cancer (MBC), and provide potential therapeutic options for patients with multidrug resistant tumors.

[681]

TÍTULO / TITLE: - [177Lu-EC0800 Combined with the Antifolate Pemetrexed: Preclinical Pilot Study of Folate Receptor Targeted Radionuclide Tumor Therapy.](#)

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0422-T](#)

AUTORES / AUTHORS: - Reber J; Haller S; Leamon CP; Mueller C

INSTITUCIÓN / INSTITUTION: - 1Center for Radiopharmaceutical Sciences, Paul Scherrer Institute.

RESUMEN / SUMMARY: - Targeted radionuclide therapy has shown impressive results for the palliative treatment of several types of cancer diseases. The folate receptor (FR) has been identified specifically associated with a variety of frequent tumor types. Therefore, it is an attractive target for the development of new radionuclide therapies using folate-based radioconjugates. Previously, we found that pemetrexed (PMX) has a favorable effect to reduce undesired renal uptake of radiofolates. Moreover, PMX also acts as a chemotherapeutic and radiosensitizing agent on tumors. Thus, the aim of our study was to investigate the combined application of PMX and the therapeutic radiofolate, 177Lu-EC0800. Determination of the combination index (CI) revealed a synergistic inhibitory effect of 177Lu-EC0800 and PMX on the viability of FR positive cervical (KB) and ovarian (IGROV-1) cancer cells in vitro (CI < 0.8). In an in vivo study, tumor bearing mice were treated with 177Lu-EC0800 (20 MBq) and a subtherapeutic (0.4 mg) or therapeutic amount (1.6 mg) of PMX. Application of 177Lu-EC0800 with PMXther resulted in a 2-4-fold enhanced tumor growth delay and a prolonged survival of KB and IGROV-1 tumor-bearing mice, as compared to the combination with PMXsubther or untreated control mice. PMXsubther protected the kidneys from undesired side effects of 177Lu-EC0800 (20 MBq) by reducing the absorbed radiation dose. Intact kidney function was demonstrated by determination of plasma parameters and quantitative SPECT using 99mTc-DMSA. Our results confirmed the anticipated dual role of PMX. Its unique features resulted in an improved antitumor effect of folate-based radionuclide therapy, and prevented undesired radio-nephrotoxicity.

[682]

TÍTULO / TITLE: - A novel synthetic derivative of the natural product berbamine inhibits cell viability and induces apoptosis of human osteosarcoma cells, associated with activation of JNK/AP-1 signaling.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 28;14(11).

AUTORES / AUTHORS: - Yang F; Nam S; Zhao R; Tian Y; Liu L; Horne D; Jove R

INSTITUCIÓN / INSTITUTION: - Department of Molecular Medicine; Beckman Research Institute; City of Hope Comprehensive Cancer Center; Duarte, CA USA.

RESUMEN / SUMMARY: - Osteosarcoma is the most common primary bone tumor in children and adolescents. There is a critical need to find more potent drugs for patients with metastatic or recurrent disease. Berbamine (BBM) is a natural compound derived from the Berberis amurensis plants. BBM and its derivatives have been shown to have antitumor effects in several cancers. Here, we report that a novel synthetic berbamine derivative, BBMD3, inhibits cell viability and induces apoptosis of G292, KHOS, and MG-63 human osteosarcoma cells. Induction of apoptosis in these tumor cells depends on activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase (PARP). Since pan-caspase inhibitor (Z-VAD-FMK) and caspase-9 inhibitor (Z-LEHD-FMK) could block the cleavage of PARP, the apoptosis induced by BBMD3 is through intrinsic signaling pathway. BBMD3 increased phosphorylation of c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK), resulting in increase of phosphorylated c-Jun and total c-Fos, the major components of transcriptional factor AP-1. JNK inhibitor could partially suppress antitumor effect of BBMD3 on osteosarcoma cells. BBMD3 increased the production of reactive oxygen species (ROS) and ROS scavenger, N-acetylcysteine (NAC), could block the phosphorylation of JNK and c-Jun induced by BBMD3. BBMD3 increased the expression of the pro-apoptotic gene Bad, associated with apoptosis induction. Finally, BBMD3 also decreased the expression of cyclin D1 and D2, the positive cell cycle regulators, which is correlated with growth inhibition in osteosarcoma cells. Collectively, these findings indicate that BBMD3 is a potentially promising drug for the treatment of human osteosarcoma.

[683]

TÍTULO / TITLE: - Integrative prediction of gene function and platinum-free survival from genomic and epigenetic features in ovarian cancer.

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

REVISTA / JOURNAL: - Methods Mol Biol. 2013;1049:35-51. doi: 10.1007/978-1-62703-547-7_4.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-62703-547-7 4](#)

AUTORES / AUTHORS: - Wrzeszczynski KO; Varadan V; Kamalakaran S; Levine DA; Dimitrova N; Lucito R

INSTITUCIÓN / INSTITUTION: - Bioinformatics and Genomics, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA.

RESUMEN / SUMMARY: - The identification of genetic and epigenetic alterations from primary tumor cells has become a common method to discover genes critical to the development, progression, and therapeutic resistance of cancer. We seek to identify those genetic and epigenetic aberrations that have the most impact on gene function within the tumor. First, we perform a bioinformatics analysis of copy number variation (CNV) and DNA methylation covering the genetic landscape of ovarian cancer tumor cells. We were specifically interested in copy number variation as our base genomic property in the prediction of tumor suppressors and oncogenes in the altered ovarian tumor. We identify changes in DNA methylation and expression specifically for all amplified and deleted genes. We statistically define tumor suppressor and oncogenic gene function from integrative analysis of three modalities: copy number variation, DNA methylation, and gene expression. Our method (1) calculates the extent of genomic and epigenetic alterations of defined tumor suppressor and oncogenic features for the functional prediction of significant ovarian cancer gene candidates and (2) identifies the functional activity or inactivity of known tumor suppressors and oncogenes in ovarian cancer. We applied our protocol on 42 primary serous ovarian cancer samples using MOMA-ROMA representational array assays. Additionally, we provide the basis for incorporating epigenetic profiles of ovarian tumors for the purposes of platinum-free survival prediction in the context of TCGA data.

[684]

TÍTULO / TITLE: - Sphingosine Kinase-1 Activation Causes Acquired Resistance Against Sunitinib in Renal Cell Carcinoma Cells.

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

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1007/s12013-013-9723-4](#)

AUTORES / AUTHORS: - Gao H; Deng L

INSTITUCIÓN / INSTITUTION: - Medical College, Qingdao University, Qingdao, 266023, Shandong, China.

RESUMEN / SUMMARY: - Multi-target tyrosine kinase inhibitor Sunitinib has been widely used in cancer treatment, including metastatic renal cell carcinoma. However, most patients who initially benefit from Sunitinib develop resistance with extended usage of Sunitinib, which is referred to as “acquired resistance”. The molecular mechanisms contributing to this acquired resistance remain poorly understood. In this present study, we established Sunitinib-resistant cell lines from human renal cell lines (786-O, A498, ACHN and CAKI1) by continuous treatment with Sunitinib to explore the

molecular mechanism leading to Sunitinib resistance. We found that PDGFR-beta expression in cell seems to be a protective factor against Sunitinib resistance formation. In addition, we found that both SK1 and ERK were activated in Sunitinib-resistance cell lines and SK1 and ERK inhibitors could resensitize Sunitinib-resistant cell lines. In conclusion, our observations suggest that SK1 and ERK activation is a feature of resistant cell lines, which serves as an alternative pathway evading anti-tumor activity of Sunitinib.

[685]

TÍTULO / TITLE: - Mechanical regulation of cancer cell apoptosis and autophagy: Roles of bone morphogenetic protein receptor, Smad1/5, and p38 MAPK.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Sep 8;1833(12):3124-3133. doi: 10.1016/j.bbamcr.2013.08.023.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bbamcr.2013.08.023](#)

AUTORES / AUTHORS: - Lien SC; Chang SF; Lee PL; Wei SY; Chang MD; Chang JY; Chiu JJ

INSTITUCIÓN / INSTITUTION: - Institute of Cellular and System Medicine, National Health Research Institutes, Miaoli, Taiwan; Institute of Molecular and Cellular Biology, Department of Medical Science, National Tsing-Hua University, Hsinchu, Taiwan.

RESUMEN / SUMMARY: - Mechanical forces induced by interstitial fluid flow in and surrounding tissues and by blood/lymphatic flow in vessels may modulate cancer cell invasion and metastasis and anticancer drug delivery. Our previous study demonstrated that laminar flow-induced shear stress induces G2/M arrest in tumor cells. However, whether shear stress modulates final cell fate remains unclear. In this study, we investigated the role of flow-induced shear stress in modulating the survival of four human tumor cell lines, i.e., Hep3B hepatocarcinoma cells, MG63 osteosarcoma cells, SCC25 oral squamous carcinoma cells, and A549 carcinomic alveolar basal epithelial cells. Laminar shear stress (LSS) ranging from 0.5 to 12 dyn/cm² induced death of these four tumor cell lines. In contrast to LSS at 0.5 dyn/cm², oscillatory shear stress (OSS) at 0.5 +/- 4 dyn/cm² cannot induce cancer cell death. Both LSS and OSS had no effect on human normal hepatocyte, lung epithelial, and endothelial cells. Application of LSS to these four cell lines increased the percentage of cells stained positively for annexin V-FITC, with up-regulations of cleaved caspase-8, -9, and -3, and PARP. In addition, LSS also induced Hep3B cell autophagy, as detected by acidic vesicular organelle formation, LC3B transformation, and p62/SQSTM1 degradation. By transfecting with small interfering RNA, we found that the shear-induced apoptosis and autophagy are mediated by bone morphogenetic protein receptor type (BMPR)-IB, BMPR-specific Smad1 and Smad5, and p38 mitogen-activated protein kinase in Hep3B cells. Our findings provide insights into the

molecular mechanisms by which shear stress induces apoptosis and autophagy in tumor cells.

[686]

TÍTULO / TITLE: - Negative modulation of mitochondrial oxidative phosphorylation by epigallocatechin-3 gallate leads to growth arrest and apoptosis in human malignant pleural mesothelioma cells.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 2;1832(12):2085-2096. doi: 10.1016/j.bbadis.2013.07.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbadis.2013.07.014](https://doi.org/10.1016/j.bbadis.2013.07.014)

AUTORES / AUTHORS: - Valenti D; de Bari L; Manente GA; Rossi L; Mutti L; Moro L; Vacca RA

INSTITUCIÓN / INSTITUTION: - Institute of Biomembranes and Bioenergetics, National Council of Research, Bari, Italy. Electronic address: d.valenti@ibbe.cnr.it.

RESUMEN / SUMMARY: - Increasing evidence reveals a large dependency of epithelial cancer cells on oxidative phosphorylation (OXPHOS) for energy production. In this study we tested the potential of epigallocatechin-3-gallate (EGCG), a natural polyphenol known to target mitochondria, in inducing OXPHOS impairment and cell energy deficit in human epitheliod (REN cells) and biphasic (MSTO-211H cells) malignant pleural mesothelioma (MMe), a rare but highly aggressive tumor with high unmet need for treatment. Due to EGCG instability that causes H₂O₂ formation in culture medium, the drug was added to MMe cells in the presence of exogenous superoxide dismutase and catalase, already proved to stabilize the EGCG molecule and prevent EGCG-dependent reactive oxygen species formation. We show that under these experimental conditions, EGCG causes the selective arrest of MMe cell growth with respect to normal mesothelial cells and the induction of mitochondria-mediated apoptosis, as revealed by early mitochondrial ultrastructure modification, swelling and cytochrome c release. We disclose a novel mechanism by which EGCG induces apoptosis through the impairment of mitochondrial respiratory chain complexes, particularly of complex I, II and ATP synthase. This induces a strong reduction in ATP production by OXPHOS, that is not adequately counterbalanced by glycolytic shift, resulting in cell energy deficit, cell cycle arrest and apoptosis. The EGCG-dependent negative modulation of mitochondrial energy metabolism, selective for cancer cells, gives an important input for the development of novel pharmacological strategies for MMe.

[687]

TÍTULO / TITLE: - PARP and CHK inhibitors interact to cause DNA damage and cell death in mammary carcinoma cells.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 May;14(5):458-65. doi: 10.4161/cbt.24424.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.24424](#)

AUTORES / AUTHORS: - Booth L; Cruickshanks N; Ridder T; Dai Y; Grant S; Dent P

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Virginia Commonwealth University, Richmond, VA, USA.

RESUMEN / SUMMARY: - The present studies examined viability and DNA damage levels in mammary carcinoma cells following PARP1 and CHK1 inhibitor drug combination exposure. PARP1 inhibitors [AZD2281 ; ABT888 ; NU1025 ; AG014699] interacted with CHK1 inhibitors [UCN-01 ; AZD7762 ; LY2603618] to kill mammary carcinoma cells. PARP1 and CHK1 inhibitors interacted to increase both single strand and double strand DNA breaks that correlated with increased gammaH2AX phosphorylation. Treatment of cells with CHK1 inhibitors increased the phosphorylation of CHK1 and ERK1/2. Knock down of ATM suppressed the drug-induced increases in CHK1 and ERK1/2 phosphorylation and enhanced tumor cell killing by PARP1 and CHK1 inhibitors. Expression of dominant negative MEK1 enhanced drug-induced DNA damage whereas expression of activated MEK1 suppressed both the DNA damage response and tumor cell killing. Collectively our data demonstrate that PARP1 and CHK1 inhibitors interact to kill mammary carcinoma cells and that increased DNA damage is a surrogate marker for the response of cells to this drug combination.

[688]

TÍTULO / TITLE: - DNA Repair Gene Patterns as Prognostic and Predictive Factors in Molecular Breast Cancer Subtypes.

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

REVISTA / JOURNAL: - Oncologist. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1634/theoncologist.2013-0163](#)

AUTORES / AUTHORS: - Santarpia L; Iwamoto T; Di Leo A; Hayashi N; Bottai G; Stampfer M; Andre F; Turner NC; Symmans WF; Hortobagyi GN; Pusztai L; Bianchini G

INSTITUCIÓN / INSTITUTION: - Translational Research Unit, Department of Oncology, Istituto Toscano Tumori, Prato, Italy;

RESUMEN / SUMMARY: - DNA repair pathways can enable tumor cells to survive DNA damage induced by chemotherapy and thus provide prognostic and/or predictive value. We evaluated Affymetrix gene expression profiles for 145 DNA repair genes in untreated breast cancer (BC) patients (n = 684) and BC patients treated with regimens containing neoadjuvant taxane/anthracycline (n = 294) or anthracycline (n = 210). We independently assessed estrogen receptor (ER)-positive/HER2-negative, HER2-positive,

and ER-negative/HER2-negative subgroups for differential expression, bimodal distribution, and the prognostic and predictive value of DNA repair gene expression. Twenty-two genes were consistently overexpressed in ER-negative tumors, and five genes were overexpressed in ER-positive tumors, but no differences in expression were associated with HER2 status. In ER-positive/HER2-negative tumors, the expression of nine genes (BUB1, FANCI, MNAT1, PARP2, PCNA, POLQ, RPA3, TOP2A, and UBE2V2) was associated with poor prognosis, and the expression of one gene (ATM) was associated with good prognosis. Furthermore, the prognostic value of specific genes did not correlate with proliferation. A few genes were associated with chemotherapy response in BC subtypes and treatment-specific manner. In ER-negative/HER2-negative tumors, the MSH2, MSH6, and FAN1 (previously MTMR15) genes were associated with pathological complete response and residual invasive cancer in taxane/anthracycline-treated patients. Conversely, PMS2 expression was associated with residual invasive cancer in treatments using anthracycline as a single agent. In HER2-positive tumors, TOP2A was associated with patient response to anthracyclines but not to taxane/anthracycline regimens. In genes expressed in a bimodal fashion, RECQL4 was significantly associated with clinical outcome. In vitro studies showed that defects in RECQL4 impair homologous recombination, sensitizing BC cells to DNA-damaging agents.

[689]

TÍTULO / TITLE: - Amplification of distant estrogen response elements deregulates target genes associated with tamoxifen resistance in breast cancer.

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

REVISTA / JOURNAL: - Cancer Cell. 2013 Aug 12;24(2):197-212. doi: 10.1016/j.ccr.2013.07.007.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ccr.2013.07.007](#)

AUTORES / AUTHORS: - Hsu PY; Hsu HK; Lan X; Juan L; Yan PS; Labanowska J; Heerema N; Hsiao TH; Chiu YC; Chen Y; Liu Y; Li L; Li R; Thompson IM; Nephew KP; Sharp ZD; Kirma NB; Jin VX; Huang TH

RESUMEN / SUMMARY: - A causal role of gene amplification in tumorigenesis is well known, whereas amplification of DNA regulatory elements as an oncogenic driver remains unclear. In this study, we integrated next-generation sequencing approaches to map distant estrogen response elements (DEREs) that remotely control the transcription of target genes through chromatin proximity. Two densely mapped DERE regions located on chromosomes 17q23 and 20q13 were frequently amplified in estrogen receptor-alpha-positive luminal breast cancer. These aberrantly amplified DEREs deregulated target gene expression potentially linked to cancer development and tamoxifen resistance. Progressive accumulation of DERE copies was observed in normal breast progenitor cells chronically exposed to estrogenic chemicals. These

findings may extend to other DNA regulatory elements, the amplification of which can profoundly alter target transcriptome during tumorigenesis.

[690]

TÍTULO / TITLE: - Binding and isolation of tumor cells in biological media with perfluorocarbon microbubbles.

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

REVISTA / JOURNAL: - Methods. 2013 Aug 22. pii: S1046-2023(13)00306-X. doi: 10.1016/j.ymeth.2013.08.008.

●● Enlace al texto completo (gratis o de pago) [1016/j.ymeth.2013.08.008](https://doi.org/10.1016/j.ymeth.2013.08.008)

AUTORES / AUTHORS: - Shi G; Cui W; Mukthavaram R; Liu YT; Simberg D

INSTITUCIÓN / INSTITUTION: - Solid Tumor Therapeutics Program, Moores UCSD Cancer Center, UC San Diego, La Jolla, CA 92093, USA.

RESUMEN / SUMMARY: - With the emerging interest in personalized medicine, there is strong demand for new technologies for clinical sample interrogation. Exfoliated tumor cells in variety of pathological samples (e.g., blood, bone marrow, urine) could provide invaluable information for diagnosis and prognosis of cancers. Here we describe a detailed method for capture and isolation of tumor cells in medium, blood, or large issue buffy coat using EpCAM-targeted buoyant microbubbles (MBs). Perflorohexane gas lipid shell MBs were prepared with emulsification method and conjugated with antibody as described by us before [25]. The binding of EpCAM-targeted MBs to A549 (human lung carcinoma) and 4T1 (mouse breast carcinoma) cells spiked into BSA/PBS or blood was more than 90%, which was comparable with commercial anti-EpCAM immunomagnetic beads (DynaBeads). Anti-EpCAM MBs efficiently (75-82%) isolated BxPC3 pancreatic tumor cells spiked into medium, blood or a buffy coat, within 15-30min of incubation. We discuss MB parameters and experimental conditions critical to achieve efficient cells binding and isolation. In conclusion, MB-assisted cell isolation is a promising method for rapid enrichment of cells and biomarkers from biological samples.

[691]

TÍTULO / TITLE: - Mitogen-activated protein kinase phosphatase-1 inhibition and sustained extracellular signal-regulated kinase ½ activation in camptothecin-induced human colon cancer cell death.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 28;14(11).

AUTORES / AUTHORS: - Lee M; Young Kim S; Kim J; Kim HS; Kim SM; Kim EJ

INSTITUCIÓN / INSTITUTION: - Division of Radiation Effect; Korea Institute of Radiological & Medical Sciences; Seoul, Korea.

RESUMEN / SUMMARY: - Camptothecins are commonly used chemotherapeutics; in some models, they enhance signaling via the mitogen-activated protein kinase (MAPK) pathway through effects on upstream kinases. To evaluate the impact of camptothecin (CPT) on MAPKs in human colon cancer, we studied HCT116 and CaCo2 colon cancer cells. We found that HCT116 cells highly express mitogen-activated protein kinase phosphatase-1 (MKP1), which selectively inactivates extracellular signal-regulated kinase (ERK), whereas MKP1 levels were undetectable in CaCo2 cells. CPT did not affect ERK activity in CaCo2 cells, but did induce a striking increase in ERK activity in HCT116 cells in association with a corresponding decrease in MKP1. The reduction in MKP1 expression occurred at a post-transcriptional level and was blocked by the proteasome inhibitor MG132, whereas that CPT-induced downregulation of MKP1 was not due to proteasome-mediated degradation. Treatment of HCT116 cells with CPT induced a sustained activation of nuclear ERK, which was required for CPT-induced apoptosis. P38 and JNK activity were unaffected by CPT, suggesting that the effects of CPT are mediated specifically by ERK. These results suggest that targeting dual-specificity MAPK phosphatases in colon cancer cells may be a viable strategy for optimizing camptothecin-based therapeutic protocols.

[692]

TÍTULO / TITLE: - Combined p21-activated kinase and farnesyltransferase inhibitor treatment exhibits enhanced anti-proliferative activity on melanoma, colon and lung cancer cell lines.

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

REVISTA / JOURNAL: - Mol Cancer. 2013 Aug 6;12(1):88. doi: 10.1186/1476-4598-12-88.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-88](#)

AUTORES / AUTHORS: - Porcu G; Parsons AB; Di Giandomenico D; Lucisano G; Mosca MG; Boone C; Ragnini-Wilson A

INSTITUCIÓN / INSTITUTION: - Department of Translational Pharmacology, Consorzio Mario Negri Sud, S, Maria Imbaro, Italy. ragnini@negrisud.it.

RESUMEN / SUMMARY: - BACKGROUND: Farnesyltransferase inhibitors (FTIs) are anticancer agents with a spectrum of activity in Ras-dependent and independent tumor cellular and xenograph models. How inhibition of protein farnesylation by FTIs results in reduced cancer cell proliferation is poorly understood due to the multiplicity of potential FTase targets. The low toxicity and oral availability of FTIs led to their introduction into clinical trials for the treatment of breast cancer, hematopoietic malignancy, advanced solid tumor and pancreatic cancer treatment, and Hutchinson-Gilford Progeria Syndrome. Although their efficacy in combinatorial therapies with conventional anticancer treatment for myeloid malignancy and solid tumors is promising, the overall results of clinical tests are far below expectations. Further exploitation of FTIs in the clinic will strongly rely on understanding how these drugs

affect global cellular activity. **METHODS:** Using FTase inhibitor I and genome-wide chemical profiling of the yeast barcoded deletion strain collection, we identified genes whose inactivation increases the antiproliferative action of this FTI peptidomimetic. The main findings were validated in a panel of cancer cell lines using FTI-277 in proliferation and biochemical assays paralleled by multiparametric image-based analyses. **RESULTS:** ABC transporter Pdr10 or p-21 activated kinase (PAK) gene deletion increases the antiproliferative action of FTase inhibitor I in yeast cells. Consistent with this, enhanced inhibition of cell proliferation by combining group I PAK inhibition, using IPA3, with FTI-277 was observed in melanoma (A375MM), lung (A549) and colon (HT29), but not in epithelial (HeLa) or breast (MCF7), cancer cell lines. Both HeLa and A375MM cells show changes in the nuclear localization of group 1 PAKs in response to FTI-277, but up-regulation of PAK protein levels is observed only in HeLa cells. **CONCLUSIONS:** Our data support the view that group I PAKs are part of a pro-survival pathway activated by FTI treatment, and group I PAK inactivation potentiates the anti-proliferative action of FTIs in yeast as well as in cancer cells. These findings open new perspectives for the use of FTIs in combinatorial strategies with PAK inhibitors in melanoma, lung and colon malignancy.

[693]

TÍTULO / TITLE: - 3,5-Diiodo-L-thyronine induces SREBP-1 proteolytic cleavage block and apoptosis in human hepatoma (HepG2) cells.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 13. pii: S1388-1981(13)00163-7. doi: 10.1016/j.bbali.2013.08.003.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.bbali.2013.08.003](#)

AUTORES / AUTHORS: - Rochira A; Damiano F; Marsigliante S; Gnoni GV; Siculella L

INSTITUCIÓN / INSTITUTION: - Laboratory of Biochemistry and Molecular Biology, Department of Biological and Environmental Science and Technologies, University of Salento, Via Prov. le Lecce-Monteroni, Lecce 73100, Italy.

RESUMEN / SUMMARY: - Thyroid hormone 3,5,3'-triiodo-L-thyronine (T3) is known to affect cell metabolism through both the genomic and non-genomic actions. Recently, we demonstrated in HepG2 cells that T3 controls the expression of SREBP-1, a transcription factor involved in the regulation of lipogenic genes. This occurs by activation of a cap-independent translation mechanism of its mRNA. Such a process is dependent on non-genomic activation of both MAPK/ERK and PI3K/Akt pathways. The physiological role of 3,5-diiodo-L-thyronine (T2), previously considered only as a T3 catabolite, is of growing interest. Evidences have been reported that T2 rapidly affects some metabolic pathways through non-genomic mechanisms. Here, we show that T2, unlike T3, determines the block of proteolytic cleavage of SREBP-1 in HepG2 cells, without affecting its expression at the transcriptional or translational level.

Consequently, Fatty Acid Synthase expression is reduced. T2 effects depend on the concurrent activation of MAPKs ERK and p38, of Akt and PKC-delta pathways. Upon the activation of these signals, apoptosis of HepG2 cells seems to occur, starting at 12h of T2 treatment. PKC-delta appears to act as a switch between p38 activation and Akt suppression, suggesting that this PKC may function as a controller in the balance of pro-apoptotic (p38) and anti-apoptotic (Akt) signals in HepG2 cells.

[694]

TÍTULO / TITLE: - Enhanced apoptotic effects of dihydroartemisinin-aggregated gelatin and hyaluronan nanoparticles on human lung cancer cells.

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

REVISTA / JOURNAL: - J Biomed Mater Res B Appl Biomater. 2013 Sep 11. doi: 10.1002/jbm.b.33023.

●● Enlace al texto completo (gratuito o de pago) [1002/jbm.b.33023](#)

AUTORES / AUTHORS: - Sun Q; Teong B; Chen IF; Chang SJ; Gao J; Kuo SM

INSTITUCIÓN / INSTITUTION: - Zhejiang Provincial Key Laboratory of Medical Genetics, School of Life Sciences, Wenzhou Medical College, Wenzhou, China.

RESUMEN / SUMMARY: - Recent studies suggest that dihydroartemisinin (DHA), a derivative of artemisinin isolated from the traditional Chinese herb *Artemisia annua* L., has anticancer properties. Due to poor water solubility, poor oral activity, and a short plasma half-life, large doses of DHA have to be injected to achieve the necessary bioavailability. This study examined increasing DHA bioavailability by encapsulating DHA within gelatin (GEL) or hyaluronan (HA) nanoparticles via an electrostatic field system. Observations from transmission electron microscopy show that DHA in GEL and HA nanoparticles formed GEL/DHA and HA/DHA aggregates that were approximately 30-40 nm in diameter. The entrapment efficiencies for DHA were approximately 13 and 35% for the GEL/DHA and HA/DHA aggregates, respectively. The proliferation of A549 cells was inhibited by the GEL/DHA and HA/DHA aggregates. Fluorescent annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) staining displayed low background staining with annexin V-FITC or PI on DHA-untreated cells. In contrast, annexin V-FITC and PI stains dramatically increased when the cells were incubated with GEL/DHA and HA/DHA aggregates. These results suggest that DHA-aggregated GEL and HA nanoparticles exhibit higher anticancer proliferation activities than DHA alone in A549 cells most likely due to the greater aqueous dispersion after hydrophilic GEL or HA nanoparticles aggregation. These results demonstrate that DHA can aggregate with nanoparticles in an electrostatic field environment to form DHA nanosized aggregates. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2013.

[695]

TÍTULO / TITLE: - Simultaneous knock-down of Bcl-xL and Mcl-1 induces apoptosis through Bax activation in pancreatic cancer cells.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 14;1833(12):2980-2987. doi: 10.1016/j.bbamcr.2013.08.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbamcr.2013.08.006](#)

AUTORES / AUTHORS: - Takahashi H; Chen MC; Pham H; Matsuo Y; Ishiguro H; Reber HA; Takeyama H; Hines OJ; Eibl G

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

RESUMEN / SUMMARY: - Anti-apoptotic Bcl-2 family proteins have been reported to play an important role in apoptotic cell death of human malignancies. The aim of this study was to delineate the mechanism of anti-apoptotic Bcl-2 family proteins in pancreatic cancer (PaCa) cell survival. We first analyzed the endogenous expression and subcellular localization of anti-apoptotic Bcl-2 family proteins in six PaCa cell lines by Western blot. To delineate the functional role of Bcl-2 family proteins, siRNA-mediated knock-down of protein expression was used. Apoptosis was measured by Cell Death ELISA and Hoechst 33258 staining. In the results, the expression of anti-apoptotic Bcl-2 family proteins varied between PaCa cell lines. Mcl-1 knock-down resulted in marked cleavage of PARP and induction of apoptosis. Down-regulation of Bcl-2 or Bcl-xL had a much weaker effect. Simultaneous knock-down of Bcl-xL and Mcl-1 strongly induced apoptosis, but simultaneous knock-down of Bcl-xL/Bcl-2 or Mcl-1/Bcl-2 had no additive effect. The apoptosis-inducing effect of simultaneous knock-down of Bcl-xL and Mcl-1 was associated with translocation of Bax from the cytosol to the mitochondrial membrane, cytochrome c release, and caspase activation. These results demonstrated that Bcl-xL and Mcl-1 play an important role in pancreatic cancer cell survival. Targeting both Bcl-xL and Mcl-1 may be an intriguing therapeutic strategy in PaCa.

[696]

TÍTULO / TITLE: - Hispidulin Induces Apoptosis Through Mitochondrial Dysfunction and Inhibition of P13k/Akt Signalling Pathway in HepG2 Cancer Cells.

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

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1007/s12013-013-9762-x](#)

AUTORES / AUTHORS: - Gao H; Wang H; Peng J

INSTITUCIÓN / INSTITUTION: - Medical College, Qingdao University, Qingdao, 266021, Shandong, China, amethystgh@hotmail.com.

RESUMEN / SUMMARY: - Hispidulin is a flavonoid compound which is an active ingredient in a number of traditional Chinese medicinal herbs. However, its therapeutic activity remains poorly understood. The present study investigated the pro-apoptotic effects and mechanism by which Hispidulin induces apoptosis in human hepatoblastoma cancer (HepG2) cells. The results showed that Hispidulin induced cell death in a dose- and time-dependent manner in HepG2 cells whereas no toxic reaction was observed in normal human liver cells at indicated concentration. This study also demonstrated that Hispidulin induces apoptosis through mitochondrial dysfunction, which is characterized by decreased Bcl-2/Bax ratio, disrupted mitochondrial membrane potential and increased release of cytochrome C and activated caspase-3. Our results also showed that mitochondrial dysfunction was triggered by Hispidulin-induced excessive ROS generation. Hispidulin also significantly inhibited Akt activation. ROS inhibitor NAC abrogated the inhibitory effect of Hispidulin on P13k/Akt signalling pathway and the proapoptotic effect in HepG2 cells. Our results demonstrate for the first time that Hispidulin induces apoptosis in HepG2 cells and suggested that the pro-apoptotic effect of Hispidulin was mediated through mitochondrial dysfunction and inhibition of P13k/Akt signalling pathway. Since no toxic effect was observed when normal liver cells were treated with Hispidulin, Hispidulin may have the potential to be used as therapeutic for liver cancer.

[697]

TÍTULO / TITLE: - In human retinoblastoma Y79 cells okadaic acid-parthenolide co-treatment induces synergistic apoptotic effects, with PTEN as a key player.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 12;14(10).

AUTORES / AUTHORS: - Di Fiore R; Drago-Ferrante R; D'Anneo A; Augello G; Carlisi D; De Blasio A; Giuliano M; Tesoriere G; Vento R

INSTITUCIÓN / INSTITUTION: - Laboratory of Biochemistry; Department of Biological, Chemical and Pharmaceutical Sciences and Technologies; University of Palermo, Polyclinic; Palermo, Italy.

RESUMEN / SUMMARY: - Retinoblastoma is the most common intraocular malignancy of childhood. In developing countries, treatment is limited, long-term survival rates are low and current chemotherapy causes significant morbidity to pediatric patients and significantly limits dosing. Therefore there is an urgent need to identify new therapeutic strategies to improve the clinical outcome of patients with retinoblastoma. Here, we investigated the effects of two natural compounds okadaic acid (OKA) and parthenolide (PN) on human retinoblastoma Y79 cells. For the first time we showed that OKA/PN combination at subtoxic doses induces potent synergistic apoptotic effects accompanied by lowering in p-Akt levels, increasing in the stabilized forms of p53 and potent decrease in pS166-Mdm2. We also showed the key involvement of

PTEN which, after OKA/PN treatment, potently increased before p53, thus suggesting that p53 activation was under PTEN action. Moreover, after PTEN-knockdown p-Akt/pS166Mdm2 increased over basal levels and p53 significantly lowered, while OKA/PN treatment failed both to lower p-Akt and pS166-Mdm2 and to increase p53 below/over their basal levels respectively. OKA/PN treatment potently increased ROS levels whereas decreased those of GSH. Reducing cellular GSH by l-butathionine-[S,R]-sulfoximine treatment significantly anticipated the cytotoxic effect exerted by OKA/PN. Furthermore, the effects of OKA/PN treatment on both GSH content and cell viability were less pronounced in PTEN silenced cells than in control cells. The results provide strong suggestion for combining a treatment approach that targets the PTEN/Akt/Mdm2/p53 pathway.

[698]

TÍTULO / TITLE: - Apoptosis-related gene expression in glioblastoma (LN-18) and medulloblastoma (Daoy) cell lines.

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

REVISTA / JOURNAL: - Hum Cell. 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1007/s13577-011-0029-9](#)

AUTORES / AUTHORS: - Wybranska I; Polus A; Mikolajczyk M; Knapp A; Sliwa A; Zapala B; Staszal T; Dembinska-Kiec A

INSTITUCIÓN / INSTITUTION: - Department of Genetic Diagnostics and Nutrigenomics, Chair of Clinical Biochemistry, The Jagiellonian University, Medical College, Krakow, Poland, mbwybran@cyf-kr.edu.pl.

RESUMEN / SUMMARY: - The expression of apoptosis genes in a commercial pre-designed low-density array from Applied Biosystems was evaluated in two human brain cancer cell models, LN-18 and Daoy (HTB-186) in comparison to the reference human primary endothelial cells under basic conditions. Analysis of the gene expression in the cancer cell lines compared to the normal control revealed features reflecting anti-apoptotic and inflammatory characteristics of the former. There was an overall downregulation of apoptosis-stimulating genes in both cancer cell lines, along with an upregulation of certain apoptosis inhibitors. A number of genes demonstrated statistically significant changes in their expressions, including BAX (BCL2-associated X protein); the CARD4/NLR family, CARD domain containing 4; CASP10 (caspase 10, apoptosis-related cysteine peptidase); DAP1 (death-associated protein kinase 1), and BIRC5 (baculoviral IAP repeat-containing 5). Anti-apoptotic potential in both cell lines was demonstrated by changes in the Bax:Bcl-2 ratio and downregulation of the APAF1 gene in LN18 cells. There was also significant downregulation of extrinsic signals and the TNF/FADD/inflammatory cascade, and upregulation of caspase inhibitors (IAPs). These results provided a novel molecular characterization of important human cancer cell

lines, which might provide a useful research tool for investigating the experimental model of the CNS cell.

[699]

TÍTULO / TITLE: - Tumor necrosis factor-like weak inducer of apoptosis and its receptor fibroblast growth factor-inducible 14 are expressed in urticarial vasculitis.

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

REVISTA / JOURNAL: - J Dermatol. 2013 Aug 23. doi: 10.1111/1346-8138.12251.

●● Enlace al texto completo (gratis o de pago) [1111/1346-8138.12251](#)

AUTORES / AUTHORS: - Li M; Chen T; Guo Z; Li J; Cao N

INSTITUCIÓN / INSTITUTION: - Department of Dermatovenereology, West China Hospital of Sichuan University, Chengdu, China.

RESUMEN / SUMMARY: - Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), a member of the TNF family, has been implicated as a pro-inflammatory cytokine in many types of autoimmune and infectious diseases. However, information about TWEAK in dermatological diseases is limited. To date, no studies have investigated the roles of TWEAK in patients with urticarial vasculitis (UV). This study aimed to assess serum TWEAK levels, together with TWEAK and fibroblast growth factor-inducible 14 (Fn14) expressions of skin lesions in patients with UV. Serum TWEAK levels in patients with UV, together with patients with cutaneous leukocytoclastic angiitis (CLA) and healthy controls were detected by enzyme-linked immunosorbent assay; TWEAK and Fn14 expressions of skin lesions were analyzed by immunohistochemistry. Results showed that TWEAK and Fn14 were abundantly expressed in the dermal vessel wall of lesional skin in patients with UV but not healthy controls. Serum TWEAK levels in the acute stage in patients with UV were significantly higher than those in the convalescent stage and healthy controls. Serum TWEAK levels were elevated significantly in patients with CLA compared with those in healthy controls. Our previous study indicated that TWEAK may be an important mediator for the development of vascular inflammation in skin. In addition, we also found that TWEAK blockade substantially reduced vascular damage and perivascular leukocyte infiltrates in lipopolysaccharide-induced cutaneous vasculitis. Our study shows that TWEAK may be associated with the pathogenesis of UV; it is therefore suggested that TWEAK may be a potential therapeutic target for UV and other types of cutaneous vasculitis.

[700]

TÍTULO / TITLE: - Overexpression of Asparagine Synthetase and Matrix Metalloproteinase 19 Confers Cisplatin Sensitivity in Nasopharyngeal Carcinoma Cells.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

- Enlace al texto completo (gratis o de pago) 1158/1535-7163.MCT-12-1190

AUTORES / AUTHORS: - Liu RY; Dong Z; Liu J; Zhou L; Huang W; Khoo SK; Zhang Z; Petillo D; Teh BT; Qian CN; Zhang JT

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Department of Pharmacology and Toxicology and 2IU Simon Cancer Center, Indiana University School of Medicine, Indianapolis, Indiana; 3State Key Laboratory of Oncology in South China and 4Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China; 5Laboratories of Microarray Technology, and 6Cancer Genetics, Van Andel Research Institute, Grand Rapids, Michigan; and 7NCCS-VARI Translational Research Laboratory, National Cancer Center Singapore, Singapore.

RESUMEN / SUMMARY: - Platinum-based concurrent chemoradiotherapy is considered a standard treatment approach for locoregionally advanced nasopharyngeal carcinoma. However, only a minority of patients benefit from this treatment regimen compared with radiotherapy alone. Identification of a set of molecular markers predicting sensitivity of platinum-based chemotherapy may contribute to personalized treatment of patients with nasopharyngeal carcinoma for better clinical outcome with less toxicity. Previously, we generated a cisplatin-sensitive nasopharyngeal carcinoma cell line, S16, by clonal selection from CNE-2 cells and found that eIF3a is upregulated and contributes to cisplatin sensitivity by downregulating the synthesis of nucleotide excision repair proteins. In this study, we conducted a gene expression profiling analysis and found three other genes, asparagine synthetase (ASNS), choriogonadotropin alpha subunit (CGA), and matrix metalloproteinase 19 (MMP19), that are upregulated in the cisplatin-sensitive S16 cells compared with the CNE-2 cells. However, only ASNS and MMP19, but not CGA, contributes to cisplatin sensitivity by potentiating cisplatin-induced DNA damage and apoptosis. Thus, ASNS and MMP19, along with eIF3a, are the sensitivity factors for cisplatin treatment and may serve as potential candidate molecular markers for predicting cisplatin sensitivity of advanced nasopharyngeal carcinoma. Mol Cancer Ther; 12(10); 1-10. ©2013 AACR.

[701]

TÍTULO / TITLE: - Anticancer effects of cinnamic Acid in lung adenocarcinoma cell line h1299-derived stem-like cells.

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

REVISTA / JOURNAL: - Oncol Res. 2013;20(11):499-507. doi: 10.3727/096504013X13685487925095.

- Enlace al texto completo (gratis o de pago)

3727/096504013X13685487925095

AUTORES / AUTHORS: - Huang Y; Zeng F; Xu L; Zhou J; Liu X; Le H

INSTITUCIÓN / INSTITUTION: - Joint Laboratory of Immunogenomics, Zhoushan Hospital-BIG/CAS, Zhoushan, Zhejiang, People's Republic of China.

RESUMEN / SUMMARY: - Lung cancer is a lethal solid tumor with poor prognosis because of its high metastasis and resistance to current therapies. Recently, cancer stem cells (CSCs) were suggested to be major contributors to tumorigenicity and cancer relapse. However, therapeutic targets for lung cancer-related CSCs remain undetermined. The objective of the current study was to investigate whether cinnamic acid (CINN) exerts an antitumor activity against sphere-derived lung CSCs. In this study, CSCs were isolated from the non-small cell lung cancer cell line H1299 as tumor spheres under CSC-selective conditions, and found to have increased tumorigenicity, chemoresistance, and higher expression of both embryonic stem cell-related and drug resistance-related genes compared with parental cells. These observations are consistent with the notion that CSCs are tumorigenic, display the ability to self-renew, and generate differentiated progeny that constitute the majority of cells in tumors. Treatment of sphere-derived stem cells with CINN could diminish their CSC-like abilities by decreasing their proliferation and invasive abilities and facilitating their differentiation into CD133-negative cells. Furthermore, CINN treatment increased the sensitivity of CSCs to chemotherapeutic drugs through apoptosis. Of note, xenotransplantation experiments revealed that CINN combined with cisplatin had a synergistic effect in inhibiting the tumorigenicity of CSCs. In summary, our study clearly revealed the presence of a population of sphere-forming cells with stem-like properties among H1299 cells and CINN can attenuate CSC properties of this stem-like cell population. The potential of CINN should be verified further in future studies of anti-CSC therapy.

[702]

TÍTULO / TITLE: - Combining Histone deacetylase inhibitors with MDA-7/IL-24 enhances killing of renal carcinoma cells.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 28;14(11).

AUTORES / AUTHORS: - Hamed HA; Das SK; Sokhi UK; Park MA; Cruickshanks N; Archer K; Ogretmen B; Grant S; Sarkar D; Fisher PB; Dent P

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery; Virginia Commonwealth University; Richmond, VA USA.

RESUMEN / SUMMARY: - In the present study we show that histone deacetylase inhibitors (HDACIs) enhance the anti-tumor effects of melanoma differentiation associated gene-7/interleukin 24 (mda- 7/IL-24) in human renal carcinoma cells. Similar data were obtained in other GU tumor cells. Combination of these two agents resulted in increased autophagy that was dependent on expression of ceramide synthase 6, with HDACIs enhancing MDA-7/IL-24 toxicity by increasing generation of

ROS and Ca²⁺. Knock down of CD95 protected cells from HDACi and MDA-7/IL-24 lethality. Sorafenib treatment further enhanced (HDACi + MDA-7/IL-24) lethality. Anoikis resistant renal carcinoma cells were more sensitive to MDA-7/IL-24 that correlated with elevated SRC activity and tyrosine phosphorylation of CD95. We employed a recently constructed serotype 5/3 adenovirus, which is more effective than a serotype 5 virus in delivering mda-7/IL-24 to renal carcinoma cells and which conditionally replicates (CR) in tumor cells expressing MDA-7/IL-24 by virtue of placing the adenoviral E1A gene under the control of the cancer-specific promoter progression elevated gene-3 (Ad.5/3-PEG-E1A-mda-7; CRAd.5/3-mda-7, Ad.5/3-CTV), to define efficacy in renal carcinoma cells. Ad.5/3-CTV decreased the growth of renal carcinoma tumors to a significantly greater extent than did a non-replicative virus Ad.5/3-mda-7. In contralateral uninfected renal carcinoma tumors Ad.5/3-CTV also decreased the growth of tumors to a greater extent than did Ad.5/3-mda-7. In summation, our data demonstrates that HDACi enhance MDA-7/IL-24-mediated toxicity and tumor specific adenoviral delivery and viral replication of mda-7/IL-24 is an effective pre-clinical renal carcinoma therapeutic.

[703]

TÍTULO / TITLE: - Novel off-target effect of tamoxifen - Inhibition of acid ceramidase activity in cancer cells.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 9. pii: S1388-1981(13)00161-3. doi: 10.1016/j.bbali.2013.07.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbali.2013.07.016](#)

AUTORES / AUTHORS: - Morad SA; Levin JC; Tan SF; Fox TE; Feith DJ; Cabot MC

INSTITUCIÓN / INSTITUTION: - John Wayne Cancer Institute at Saint John's Health Center, Department of Experimental Therapeutics, Santa Monica, CA 90404, USA.

RESUMEN / SUMMARY: - Acid ceramidase (AC), EC 3.5.1.23, a lysosomal enzyme, catalyzes the hydrolysis of ceramide to constituent sphingoid base, sphingosine, and fatty acid. Because AC regulates the levels of pro-apoptotic ceramide and mitogenic sphingosine-1-phosphate, it is considered an apt target in cancer therapy. The present study reveals, for the first time, that the prominent antiestrogen, tamoxifen, is a pan-effective AC inhibitor in the low, single digit micromolar range, as demonstrated in a wide spectrum of cancer cell types, prostate, pancreatic, colorectal, and breast. Prostate cancer cells were chosen for the detailed investigations. Treatment of intact PC-3 cells with tamoxifen produced time- and dose-dependent inhibition of AC activity. Tamoxifen did not impact cell viability nor did it inhibit AC activity in cell-free assays. In pursuit of mechanism of action, we demonstrate that tamoxifen induced time-, as early as 5min, and dose-dependent, as low as 5µM, increases in lysosomal membrane permeability (LMP), and time- and dose-dependent downregulation of AC

protein expression. Assessing various protease inhibitors revealed that a cathepsin B inhibitor blocked tamoxifen-elicited downregulation of AC protein; however, this action failed to restore AC activity unless assayed in a cell-free system at pH4.5. In addition, pretreatment with tamoxifen inhibited PC-3 cell migration. Toremifene, an antiestrogen structurally similar to tamoxifen, was also a potent inhibitor of AC activity. This study reveals a new, off-target action of tamoxifen that may be of benefit to enhance anticancer therapies that either incorporate ceramide or target ceramide metabolism.

[704]

TÍTULO / TITLE: - Cost-effectiveness of the 21-gene assay for guiding adjuvant chemotherapy decisions in early breast cancer.

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

REVISTA / JOURNAL: - Value Health. 2013 Jul-Aug;16(5):729-39. doi: 10.1016/j.jval.2013.03.1625. Epub 2013 Jul 1.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.jval.2013.03.1625](#)

AUTORES / AUTHORS: - Paulden M; Franek J; Pham B; Bedard PL; Trudeau M; Krahn M

INSTITUCIÓN / INSTITUTION: - Toronto Health Economics and Technology Assessment (THETA) Collaborative, University of Toronto, Toronto, ON, Canada. Electronic address: mike.paulden@theta.utoronto.ca.

RESUMEN / SUMMARY: - **OBJECTIVES:** Adjuvant chemotherapy decisions in early breast cancer are complex. The 21-gene assay can potentially aid such decisions, but costs US \$4175 per patient. Adjuvant! Online is a freely available decision aid. We evaluate the cost-effectiveness of using the 21-gene assay in conjunction with Adjuvant! Online, and of providing adjuvant chemotherapy conditional upon risk classification. **METHODS:** A probabilistic Markov decision model simulated risk classification, treatment, and the natural history of breast cancer in a hypothetical cohort of 50-year-old women with lymph node-negative, estrogen receptor- and/or progesterone receptor-positive, human epidermal growth factor receptor 2/neu-negative early breast cancer. Cost-effectiveness was considered from an Ontario public-payer perspective by deriving the lifetime incremental cost (2012 Canadian dollars) per quality-adjusted life-year (QALY) for each strategy, and the probability each strategy is cost-effective, assuming a willingness-to-pay of \$50,000 per QALY. **RESULTS:** The 21-gene assay has an incremental cost per QALY in patients at low, intermediate, or high Adjuvant Online! risk of \$22,440 (probability cost-effective 78.46%), \$2,526 (99.40%), or \$1,111 (99.82%), respectively. In patients at low (high) 21-gene assay risk, adjuvant chemotherapy increases (reduces) costs and worsens (improves) health outcomes. For patients at intermediate 21-gene assay risk and low, intermediate, or high Adjuvant! Online risk, chemotherapy has an incremental cost per QALY of \$44,088 (50.59%), \$1,776 (77.65%), or \$1,778 (82.31%), respectively. **CONCLUSIONS:** The 21-gene assay

appears cost-effective, regardless of Adjuvant! Online risk. Adjuvant chemotherapy appears cost-effective for patients at intermediate or high 21-gene assay risk, although this finding is uncertain in patients at intermediate 21-gene assay and low Adjuvant! Online risk.

PTPTPTP - Journal Article

[705]

TÍTULO / TITLE: - Oncolytic adenovirus encoding tumor necrosis factor-related apoptosis inducing ligand (TRAIL) inhibits the growth and metastasis of triple-negative breast cancer.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 28;14(11).

AUTORES / AUTHORS: - Zhu W; Zhang H; Shi Y; Song M; Zhu B; Wei L

INSTITUCIÓN / INSTITUTION: - Department of General Surgery; Zhongshan Hospital; Fudan University, Shanghai, P.R. China.

RESUMEN / SUMMARY: - Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a promising cancer therapeutic target due to its selective apoptosis-inducing effect in cancer cells. To efficiently deliver TRAIL to the tumor cells, an oncolytic adenovirus (p55-hTERT-HRE-TRAIL) carrying the TRAIL coding sequence was constructed. In the present study, we aimed to investigate the effect of p55-hTERT-HRE-TRAIL on the growth and metastasis of triple-negative breast cancer (TNBC). We observed that infection of the recombinant adenovirus resulted in expression of TRAIL and massive cell death in a TNBC cell line MDA-MB-231. This effect is much weaker in MCF-10^a, which is a normal breast cell line. Administration of P55-HTERT-HRE-TRAIL significantly reduced orthotopic breast tumor growth and extended survival in a metastatic model. Our results suggest the oncolytic adenovirus armed with P55-HTERT-HRE-TRAIL, which exhibited enhanced anti-tumor activity and improved survival, is a promising candidate for virotherapy of TNBC.

[706]

TÍTULO / TITLE: - Nanoassemblies containing a fluorouracil/zidovudine glyceryl prodrug with phospholipase A-triggered drug release for cancer treatment.

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

REVISTA / JOURNAL: - Colloids Surf B Biointerfaces. 2013 Aug 28;112C:421-428. doi: 10.1016/j.colsurfb.2013.08.021.

●● Enlace al texto completo (gratis o de pago) [1016/j.colsurfb.2013.08.021](https://doi.org/10.1016/j.colsurfb.2013.08.021)

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INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Sciences, Beijing Institute of Radiation Medicine, Beijing 100850, China; Institute of Pharmacy, Pharmaceutical

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jinyg@bmi.ac.cn.

RESUMEN / SUMMARY: - Secretory phospholipase A2 (sPLA2), which is overexpressed in many tumors, cleaves ester bonds at the sn-2 position of phospholipids. A PLA2-sensitive amphiphilic prodrug, 1-O-octadecyl-2-(5-fluorouracil)-N-acetyl-3-zidovudine-phosphorylglycerol (OFZG), was synthesized and used to prepare nanoassemblies through the injection of a mixture of OFZG/cholesterol/Tween 80 (2:1:0.1, mol:mol:mol) into water. Cholesterol and Tween 80 was incorporated into the OFZG monolayers at the air/water interface to yield nanoassemblies. The resulting nanoassemblies exhibited a narrow size distribution with a mean size of 77.8nm and were stable due to their high surface charges. The in vitro experiments showed that PLA2 degraded OFZG. The nanoassemblies exhibited higher anticancer activity than the parent drug 5-fluorouracil (5-FU) in COLO205, HT-28, and HCT-116 cells. The intravenous (i.v.) administration of the nanoassemblies into mice resulted in the rapid elimination of OFZG from the circulation and its distribution mainly in the liver, lung, spleen, and kidney. After their injection into tumor-bearing mice, the nanoassemblies exhibited anticancer efficiency comparable to that of 5-FU, even though the nanoassemblies contained concentrations of only 1/10 of the molar amount of 5-FU. The lessons learned from the study and methods for the design of PLA2-sensitive amphiphilic prodrugs are also discussed. Enzyme-sensitive amphiphilic combinatorial prodrugs and prodrug-loaded nanoassemblies may represent a new strategy for anticancer drug design.

[707]

TÍTULO / TITLE: - High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment.

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

REVISTA / JOURNAL: - J Crohns Colitis. 2013 Aug 6. pii: S1873-9946(13)00243-2. doi: 10.1016/j.crohns.2013.07.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.crohns.2013.07.005](#)

AUTORES / AUTHORS: - Magro F; Rodrigues-Pinto E; Santos-Antunes J; Vilas-Boas F; Lopes S; Nunes A; Camila-Dias C; Macedo G

INSTITUCIÓN / INSTITUTION: - Gastroenterology Department, Centro Hospitalar Sao Joao, Porto, Portugal; Institute of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Portugal; IBMC - Institute for Molecular and Cell Biology, University of Porto, Porto, Portugal. Electronic address: fm@med.up.pt.

RESUMEN / SUMMARY: - BACKGROUND: Infliximab (IFX) is effective in treating Crohn's disease (CD) and C-reactive protein (CRP) is a useful biomarker in assessing inflammatory activity. AIM: Correlate CRP levels before beginning of IFX, at week 14 and CRP delta within the first year of IFX treatment. METHODS: Retrospective study of

CD patients undergoing treatment with IFX. Primary nonresponse (PNR) was defined as no symptomatic improvement and CRP persistently elevated; sustained response (SR) as symptomatic improvement for at least 1 year without therapeutic adjustment; response after therapeutic adjustment (RTA) as analytic and clinical response but requiring IFX dose/frequency adjustment or association with another drug. RESULTS: Baseline CRP levels were higher in PNR compared with SR (26.2mg/L vs 9.6mg/L, $p=0.015$) and RTA (26.2mg/L vs 7.6mg/L, $p=0.007$). CRP levels greater than 15mg/L at baseline predict PNR with 67% sensitivity and 65% specificity. Lower CRP levels at week 14 were more likely to predict SR relative to RTA (3.1mg/L vs 7.6mg/L $p=0.019$) and PNR (3.1mg/L vs 9.1mg/L; $p=0.013$). CRP levels greater than 4.6mg/L at week 14 predict PNR with 67% sensitivity and 62% specificity. A higher CRP delta between beginning of treatment and week 14 is more likely to predict SR relative to RTA (5.2mg/L vs 0.6mg/L $p=0.027$). CONCLUSION: CRP levels at week 14 were associated with SR in patients treated with IFX, independently of baseline CRP serum levels. High inflammatory burden at beginning of IFX treatment was correlated with a worse response.

[708]

TÍTULO / TITLE: - Preoperative level of serum amyloid A is superior to C-reactive protein in the prognosis of esophageal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Dis Esophagus. 2013 Aug 30. doi: 10.1111/dote.12128.

●● [Enlace al texto completo \(gratis o de pago\) 1111/dote.12128](#)

AUTORES / AUTHORS: - Meng YQ; Cao X; Wen ZS; Liu QW; Tan ZH; Duan H; Ma GW; Lin P

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

RESUMEN / SUMMARY: - Preoperative elevations in the levels of serum amyloid A (SAA) or C-reactive protein (CRP) have been reported to be prognostic indicators in several malignancies. The aim of this study is to evaluate the serum levels of SAA and CRP in the prognosis of esophageal squamous cell carcinoma (ESCC). In total, 252 patients with ESCC who had undergone surgery with curative-intent were retrospectively recruited. The specificity, sensitivity, and prognostic value of SAA or CRP levels were measured as the area under the receiver operating characteristic (ROC) curve (AUC). The clinical value of SAA and CRP levels as prognostic indicators was evaluated using Cox's proportional hazards model. The 1-, 3-, and 5-year overall survival (OS) rates for the entire cohort of patients with ESCC were 71.0%, 61.0%, and 43.0%, respectively. The correlation between the levels of SAA and CRP was significant ($r^2 = 0.685$, $P < 0.001$). The ROC analysis showed that the levels of CRP were associated with a significantly lower overall accuracy than were the SAA levels (AUC, 0.615 vs. 0.880; $P < 0.001$). For the complete cohort, the median OS was 52.0 months longer in patients

with low preoperative serum levels of SAA (72.0 months) compared with patients who had high SAA levels (20.0 months, $P < 0.001$). The median OS among patients with low CRP levels was also longer compared with the patients who had high CRP levels (72.0 vs. 51.0 months, respectively; $P < 0.001$). Subgroup analyses showed that the preoperative elevated levels of SAA could find significant differences in OS for stage I, stage II, and stage III ($P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively), whereas the increased levels of CRP could only find a difference in OS for stage II cancers. After a multivariate analysis, preoperative elevated level of SAA was found to be an independently and significant prognostic factor ($P < 0.001$). Our study indicates that the preoperative levels of SAA and CRP can act as prognostic factors, and that elevated levels of these proteins are associated with negative effects on the survival of patients with ESCC. SAA showed a higher prognostic value than CRP in both cohort and subgroup analysis.

[709]

TÍTULO / TITLE: - Protein kinase inhibitors in melanoma.

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

REVISTA / JOURNAL: - Expert Opin Pharmacother. 2013 Aug 31.

●● [Enlace al texto completo \(gratis o de pago\) 1517/14656566.2013.827172](#)

AUTORES / AUTHORS: - Eigentler TK; Meier F; Garbe C

INSTITUCIÓN / INSTITUTION: - Center for Dermatooncology, Department of Dermatology , Liebermeisterstrasse 20, 72076 Tübingen , Germany.

RESUMEN / SUMMARY: - Introduction: The most commonly mutated oncogene identified to date in melanoma is BRAF (approximately 50%), an upstream mediator of the mitogen-activated protein kinase (MAPK) pathway. Recently, BRAF-kinase inhibitors as well as MEK-kinase inhibitors were introduced into the clinics. Areas covered: Substantial Phase II and III clinical trials were searched in patients with advanced melanoma treated with BRAF-kinase inhibitors, MEK-kinase inhibitors and cKIT inhibitors. Expert opinion: For patients with a BRAF, NRAS or cKIT mutation the treatment with selective, targeted drugs is considered as feasible and results in a high rate of confirmed tumor responses. In patients with BRAF mutation the progression free survival and overall survival is prolonged in patients who were treated with BRAF kinase inhibitors or MEK kinase inhibitors compared to patients receiving chemotherapy with dacarbazine. A major problem is the development of resistance to the inhibitors through multiple different mechanisms. One approach to overcome resistance is to combine BRAF and MEK inhibitors. Treatments with kinase inhibitors are more efficacious than chemotherapies, however, they compete with the newly developed immune checkpoint blockers, and may in future be preferentially applied in second- or x-line.

[710]

TÍTULO / TITLE: - Proteomics identified nuclear N-myc downstream-regulated gene 1 as a prognostic tissue biomarker candidate in renal cell carcinoma.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 30. pii: S1570-9639(13)00307-5. doi: 10.1016/j.bbapap.2013.08.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbapap.2013.08.009](#)

AUTORES / AUTHORS: - Hosoya N; Sakumoto M; Nakamura Y; Narisawa T; Bilim V; Motoyama T; Tomita Y; Kondo T

INSTITUCIÓN / INSTITUTION: - Division of Pharmacoproteomics, National Cancer Center Research Institute, Tokyo, Japan; Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan.

RESUMEN / SUMMARY: - The aim of this study was to identify proteins with aberrant expression in clear cell renal cell carcinoma (ccRCC), and elucidate their clinical utilities. The protein expression profiles of primary ccRCC tumor tissues and neighboring non-tumor tissues were obtained from 9 patients by two-dimensional difference gel electrophoresis and mass spectrometry. Comparative analysis of 3771 protein spots led to the identification of 73 proteins that were expressed at aberrant levels in tumor tissues compared with non-tumor tissues. Among these 73 proteins, we further focused on N-myc downstream-regulated gene 1 protein (NDRG1). NDRG1 expression is regulated by members of myc family as well as by p53, HIF1A, and SGK1. The biological and clinical significance of NDRG1 is controversial for various malignancies and no detailed studies on NDRG1 have been reported in ccRCC until our study. For the 82 newly enrolled ccRCC patients, immunohistochemical analysis revealed a significant association between nuclear NDRG1 and favorable prognosis ($p < 0.05$). Multivariate analysis demonstrated the role of NDRG1 as an independent factor of progression-free survival ($p = 0.01$). Subsequent in vitro gene suppression assay demonstrated that NDRG1 silencing significantly enhanced cell proliferation and invasion of RCC cells. The cytotoxic effects of NDRG1 up-regulation induced by an iron chelator were also confirmed. These findings suggest that nuclear NDRG1 has tumor suppressive effects, and the NDRG1 expression may have clinical values in ccRCC. Nuclear NDRG1 may provide additional insights on molecular backgrounds of ccRCC progression, and contribute to the development of novel therapeutic strategy.

[711]

TÍTULO / TITLE: - Chemotherapy With Erlotinib or Chemotherapy Alone in Advanced Non-Small Cell Lung Cancer With Acquired Resistance to EGFR Tyrosine Kinase Inhibitors.

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

REVISTA / JOURNAL: - Oncologist. 2013 Sep 26.

- Enlace al texto completo (gratuito o de pago) 1634/theoncologist.2013-0168

AUTORES / AUTHORS: - Goldberg SB; Oxnard GR; Digumarthy S; Muzikansky A; Jackman DM; Lennes IT; Sequist LV

INSTITUCIÓN / INSTITUTION: - Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA;

RESUMEN / SUMMARY: - **PURPOSE:** Epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer has an oncogene-addicted biology that confers sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Published data suggest that EGFR addiction persists after development of TKI acquired resistance, leading many clinicians to continue TKI with subsequent chemotherapy; however, this strategy has not been formally evaluated. **METHODS:** We retrospectively reviewed an institutional database to identify patients with advanced EGFR mutation with acquired resistance who subsequently received chemotherapy. Patients were classified as receiving chemotherapy with continued erlotinib or chemotherapy alone. We assessed differences in outcomes between the two strategies. **RESULTS:** Seventy-eight patients were included, 34 treated with chemotherapy and erlotinib and 44 treated with chemotherapy alone. Objective response rate was evaluable in 57 patients and was 41% for those treated with chemotherapy and erlotinib and 18% for those treated with chemotherapy alone. After adjusting for chemotherapy regimen and length of initial TKI course, the odds ratio for the response rate was 0.20 (95% confidence interval: 0.05-0.78; $p = .02$) favoring treatment with chemotherapy and erlotinib. The median progression-free survival was 4.4 months on chemotherapy and erlotinib and 4.2 months on chemotherapy alone (adjusted hazard ratio = 0.79; 95% confidence interval: 0.48-1.29; $p = .34$). There was no difference in overall survival. **CONCLUSION:** This is the first study, to our knowledge, to demonstrate that continuation of EGFR TKI with chemotherapy in patients with acquired resistance improves outcomes compared with chemotherapy alone. We observed an improved response rate but no difference in progression-free survival or overall survival. A larger prospective clinical trial is needed to evaluate this promising strategy further.

[712]

TÍTULO / TITLE: - Prognostic Role of Lemur Tyrosine Kinase-3 Germline Polymorphisms in Adjuvant Gastric Cancer in Japan and the United States.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

- Enlace al texto completo (gratuito o de pago) 1158/1535-7163.MCT-12-1134

AUTORES / AUTHORS: - Wakatsuki T; Labonte MJ; Bohanes PO; Zhang W; Yang D; Azuma M; Barzi A; Ning Y; Loupakis F; Saadat S; Volz N; Stintzing S; El-Khoueiry R; Koizumi W; Watanabe M; Shah M; Stebbing J; Giamas G; Lenz HJ

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Division of Medical Oncology, 2Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, Los Angeles, California; 3Department of Biology and Chemistry, Azusa Pacific University, Azusa, California; Departments of 4Gastroenterology and 5Surgery, Kitasato University East Hospital, Sagami-hara; 6Department of Gastroenterology, Fukushima Red Cross Hospital, Fukushima, Japan; 7Gastrointestinal Oncology Service, Memorial Sloan-Kettering Cancer Center, Cornell University, New York, New York; and 8Department of Surgery and Cancer, Division of Cancer, Imperial College, London, United Kingdom.

RESUMEN / SUMMARY: - Lemur tyrosine kinase-3 (LMTK3) was recently identified as an estrogen receptor (ER)-alpha modulator related to endocrine therapy resistance, and its polymorphisms rs9989661 (T>C) T/T genotype and rs8108419 (G>A) G/G or A/G genotype predicted improved outcomes in breast cancer. Because different predominant ER distributions link to breast and gastric cancer and little is known of the prognostic role of LMTK3 in gastric cancer, this study was carried out to clarify the prognostic role of these polymorphisms in gastric cancer. One-hundred and sixty-nine Japanese and 137 U.S. patients with localized gastric adenocarcinoma were enrolled. Genomic DNA was extracted from blood or tissue, and all samples were analyzed by PCR-based direct DNA sequencing. Overall, these polymorphisms were not associated with survival in both cohorts. When gender was considered, in multivariate analysis, harboring rs9989661 T/T genotype was associated with disease-free survival [HR, 4.37; 95% confidence interval (CI), 2.08-9.18; P < 0.0001] and overall survival (OS; HR, 3.69; 95% CI, 1.65-8.24; P = 0.0014) in the Japanese males and time to recurrence (HR, 7.29; 95% CI, 1.07-49.80; P = 0.043) in the U.S. females. Meanwhile, harboring rs8108419 G/G genotype was associated with OS in the Japanese females (HR, 3.04; 95% CI, 1.08-8.56; P = 0.035) and the U.S. males (HR, 3.39; 95% CI, 1.31-8.80; P = 0.012). The prognostic role of these polymorphisms may be negative in gastric cancer. These findings suggest that the estrogen pathway may play a prognostic role in patients with gastric cancer but this may be dependent on the regional differences both in physiology and genetic alterations of gastric cancer. *Mol Cancer Ther*; 12(10); 1-12. ©2013 AACR.

[713]

TÍTULO / TITLE: - The Prognostic Importance of Nuclear Factor kappaB and Hypoxia-inducible Factor 1alpha in Relation to the Breast Cancer Subtype and the Overall Survival.

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

REVISTA / JOURNAL: - Appl Immunohistochem Mol Morphol. 2013 Aug 16.

●● Enlace al texto completo (gratis o de pago) [1097/PAI.0b013e31829271ce](https://doi.org/10.1007/PAI.0b013e31829271ce)

AUTORES / AUTHORS: - Rajkovic-Molek K; Mustac E; Hadzisejdic I; Jonjic N

INSTITUCIÓN / INSTITUTION: - *Department of Cytology, Internal Medicine Clinic, Clinical Hospital Center daggerDepartment of Pathology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia.

RESUMEN / SUMMARY: - Breast cancer shows extensive clinical and molecular heterogeneity. Prognostic factors are very important for outcome estimation in individual patients. Nuclear factor kappaB (NF-kappaB) and hypoxia-inducible factor 1alpha (HIF-1alpha) are transcriptional factors involved in cancerogenesis and in the metastatic spread of tumor cells. The aim of this study was to evaluate the expression of NF-kappaB and HIF-1alpha and to correlate the immunohistochemical expression of these markers with the breast cancer subtype and the patient outcome. The retrospective study included 208 cases of ductal invasive breast cancers stratified by the molecular subtype according to the St. Gallen 2011 classification. The Kaplan-Meier survival curve showed that an increased mortality risk was associated with tumors belonging not to the luminal A subtypes but to the Her-2-enriched and luminal B-Her-2-positive subtypes instead ($P < 0.001$). Activation of NF-kappaB was associated with estrogen-negative tumors ($P = 0.005$). We found a better overall survival in NF-kappaB-positive tumors in the luminal A subtype ($P = 0.021$). This may be explained as a consequence of a possible tumor-suppressing effect of NF-kappaB. HIF-1alpha was related to the overall survival as a poor prognostic factor ($P = 0.036$). In our opinion, the practical relevance of NF-kappaB and HIF-1alpha expression as prognostic indicators and potential targets for specific therapies deserve further investigation.

[714]

TÍTULO / TITLE: - AKT Activation and Telomerase Reverse Transcriptase Expression are Concurrently Associated with Prognosis of Gastric Cancer.

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

REVISTA / JOURNAL: - Pathobiology. 2013 Aug 21;81(1):36-41.

●● Enlace al texto completo (gratis o de pago) [1159/000351721](https://doi.org/10.1159/000351721)

AUTORES / AUTHORS: - Sasaki T; Kuniyasu H; Luo Y; Kitayoshi M; Tanabe E; Kato D; Shinya S; Fujii K; Ohmori H; Yamashita Y

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterological Surgery, Fukuoka University School of Medicine, Fukuoka, Japan.

RESUMEN / SUMMARY: - AKT is a protein in the phosphatidylinositol-3 kinase (PI3K) pathway and associated with diverse pro-tumoral responses. Activation of the human telomere reverse transcriptase (hTERT) is one of AKT's tumorigenic effects. In this study, the significance of AKT phosphorylation and hTERT on prognosis of gastric cancer were examined. AKT activation by epidermal growth factor increased hTERT

expression and telomerase activity. In contrast, AKT inactivation by inhibitors and knockdown decreased hTERT expression and telomerase activity in MKN28 gastric cancer cells. In 40 gastric cancer tissues, significant correlations were found among the levels of phosphorylated AKT (pAKT), hTERT expression, and telomere length. The pAKT levels or the levels of pAKT/hTERT were not associated with clinicopathological parameters, including stage and nodal metastasis. However, survival rates of the pAKT-high patients or the pAKT-high and hTERT-high patients were significantly poorer than those in other patients. These findings suggest that AKT and hTERT are good molecular targets for the treatment of gastric cancer.

[715]

TÍTULO / TITLE: - Targeting focal adhesion kinase in ER+/HER2+ breast cancer improves trastuzumab response.

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

REVISTA / JOURNAL: - Endocr Relat Cancer. 2013 Aug 28;20(5):691-704. doi: 10.1530/ERC-13-0019. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1530/ERC-13-0019](#)

AUTORES / AUTHORS: - Lazaro G; Smith C; Goddard L; Jordan N; McClelland R; Barrett-Lee P; Nicholson RI; Hiscox S

INSTITUCIÓN / INSTITUTION: - School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, Cardiff, Wales CF10 3NB, UK Velindre Cancer Centre, Velindre Hospital, Whitchurch, Cardiff, UK.

RESUMEN / SUMMARY: - The HER2 transmembrane receptor is a well-characterised predictive marker for trastuzumab benefit and may be associated with decreased benefit from endocrine therapy use. Despite the clinical effectiveness of anti-HER2 agents in such cases, resistance represents a significant limiting factor. Focal adhesion kinase (FAK) plays an important role in HER2 signalling, mediating downstream Akt activation in addition to HER2 cross talk with other growth factor receptors. In this study, we investigated the therapeutic potential of FAK in oestrogen receptor-positive (ER+)/HER2+ breast cancer using the novel FAK-specific inhibitor PF4554878 ('PF878'). The activation of the FAK/HER2 signalling pathway was assessed in ER+/HER2- (MCF7 and T47D) and ER+/HER2+ (BT-474 and MDAMB361) breast cancer cells in the presence or absence of PF878 and PF878+/-trastuzumab. The effects of PF878 on cell growth as a monotherapy and in combination with trastuzumab were assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and Coulter counting with isobologram analysis to determine synergy/additive effects. FAK activation (at Y861 but not at Y397) was highest in ER+/HER2+ cells, which also demonstrated the greatest sensitivity to PF878. As a monotherapy, PF878 prevented heregulin-induced MDA361 cell migration, but had no significant effect on cell growth. The treatment of ER+/HER2+ cells with PF878 and trastuzumab in combination resulted in the

synergistic inhibition of cell proliferation. Underlying this was an abrogation of Akt activity and increased poly(ADP-ribose) polymerase cleavage, effects that were greatest in trastuzumab-refractory MDA361 cells. Collectively, these data support a role for FAK in ER+/HER2+ breast cancer, where its targeting has the potential to improve trastuzumab response. This is particularly important in the context of ER+/HER2+, trastuzumab-refractory disease, where FAK inhibition may present an important strategy to restore trastuzumab sensitivity.

[716]

TÍTULO / TITLE: - APSLAP: An Adaptive Boosting Technique for Predicting Subcellular Localization of Apoptosis Protein.

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

REVISTA / JOURNAL: - Acta Biotheor. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1007/s10441-013-9197-1](#)

AUTORES / AUTHORS: - Saravanan V; Lakshmi PT

INSTITUCIÓN / INSTITUTION: - Centre for Bioinformatics, School of Life Sciences, Pondicherry University, RK Nagar, Kalapet, Pondicherry, 605014, India, brsaran@bicpu.edu.in.

RESUMEN / SUMMARY: - Apoptotic proteins play key roles in understanding the mechanism of programmed cell death. Knowledge about the subcellular localization of apoptotic protein is constructive in understanding the mechanism of programmed cell death, determining the functional characterization of the protein, screening candidates in drug design, and selecting protein for relevant studies. It is also proclaimed that the information required for determining the subcellular localization of protein resides in their corresponding amino acid sequence. In this work, a new biological feature, class pattern frequency of physiochemical descriptor, was effectively used in accordance with the amino acid composition, protein similarity measure, CTD (composition, translation, and distribution) of physiochemical descriptors, and sequence similarity to predict the subcellular localization of apoptosis protein. AdaBoost with the weak learner as Random-Forest was designed for the five modules and prediction is made based on the weighted voting system. Bench mark dataset of 317 apoptosis proteins were subjected to prediction by our system and the accuracy was found to be 100.0 and 92.4 %, and 90.1 % for self-consistency test, jack-knife test, and tenfold cross validation test respectively, which is 0.9 % higher than that of other existing methods. Beside this, the independent data (N151 and ZW98) set prediction resulted in the accuracy of 90.7 and 87.7 %, respectively. These results show that the protein feature represented by a combined feature vector along with AdaBoost algorithm holds well in effective prediction of subcellular localization of apoptosis proteins. The user friendly web interface “APSLAP” has been constructed, which is freely available at

<http://apslap.bicpu.edu.in> and it is anticipated that this tool will play a significant role in determining the specific role of apoptosis proteins with reliability.

[717]

TÍTULO / TITLE: - Prognostic implications of EGFR and HER-2 alteration assessed by immunohistochemistry and silver in situ hybridization in gastric cancer patients following curative resection.

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

REVISTA / JOURNAL: - Gastric Cancer. 2013 Aug 17.

●● Enlace al texto completo (gratis o de pago) 1007/s10120-013-0288-0

AUTORES / AUTHORS: - Oh HS; Eom DW; Kang GH; Ahn YC; Lee SJ; Kim JH; Jang HJ; Kim EJ; Oh KH; Ahn HJ

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, GangNeung Asan Medical Center, University of Ulsan College of Medicine, Gangneung, Korea.

RESUMEN / SUMMARY: - BACKGROUND: The aim of this study was to use immunohistochemistry (IHC) and silver in situ hybridization (SISH) to evaluate alterations in EGFR and HER2 in gastric cancer in order to determine the relationship with prognosis in gastric cancer patients following curative resection. PATIENTS AND METHODS: In this study, we analyzed EGFR and HER-2 status by IHC and SISH in 254 stage I-III gastric cancer patients who underwent curative surgery. RESULTS: Thirteen cases (2.48 %) showed EGFR alteration by IHC or SISH. EGFR alteration was associated with older age ($P = 0.021$), intestinal type ($P = 0.040$) and higher stage disease ($P < 0.001$). The patients with operable state gastric cancer who had EGFR alteration had an unfavorable prognosis, and multivariate analysis confirmed that EGFR alteration was an independent unfavorable prognostic factor. Twenty-seven cases (10.6 %) showed HER-2 alteration by IHC or SISH. HER-2 alteration was associated with older age ($P = 0.006$), well or moderately differentiated histology ($P < 0.001$) and intestinal type ($P = 0.002$). CONCLUSION: HER-2 alteration is not an independent prognostic factor for curatively resectable gastric cancer. We observed EGFR alteration in a subset of cases with operable state gastric cancer and determined that it was associated with an unfavorable prognosis.

[718]

TÍTULO / TITLE: - Modern Chemotherapy Mitigates Adverse Prognostic Effect of Regional Nodal Metastases in Stage IV Colorectal Cancer.

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

REVISTA / JOURNAL: - J Gastrointest Surg. 2013 Sep 4.

●● Enlace al texto completo (gratis o de pago) 1007/s11605-013-2329-8

AUTORES / AUTHORS: - Thomay AA; Nagorney DM; Cohen SJ; Sigurdson ER; Truty MJ; Burtness B; Hall MJ; Chun YS

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA, 19111, USA.

RESUMEN / SUMMARY: - **BACKGROUND:** In colorectal cancer, the involvement of regional lymph nodes with metastasis is an established prognostic factor. The impact of the number of positive nodes on patient outcome with stage IV disease is not well defined. **METHODS:** A retrospective review was performed of 1,421 patients at two tertiary referral centers with stage IV colorectal cancer who underwent primary tumor resection. Associations between regional nodes, lymph node ratio (LNR), and overall survival (OS) from date of diagnosis were analyzed. **RESULTS:** The number of positive regional nodes and LNR correlated with multiple sites of metastases ($p < 0.001$). Survival was significantly associated with the number of positive nodes and LNR, with a median OS of 43 months with negative nodes, compared to 20 months with ≥ 7 positive nodes ($p < 0.001$). The number of regional nodal metastases correlated with OS among 400 patients undergoing resection of liver metastases ($p = 0.005$) but lost prognostic significance in the subset of 223 patients who underwent hepatectomy with perioperative oxaliplatin- or irinotecan-based chemotherapy ($p = 0.48$). **CONCLUSIONS:** In stage IV colorectal cancer, an increasing number of positive regional nodes and LNR correlate with multiple sites of metastases and poorer survival. The number of metastatic regional lymph nodes loses prognostic significance with modern chemotherapy in patients undergoing resection of liver metastases.

[719]

TÍTULO / TITLE: - High expression levels of class III beta-tubulin in resected non-small cell lung cancer patients are predictive of improved patient survival after vinorelbine-based adjuvant chemotherapy.

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

REVISTA / JOURNAL: - Oncol Lett. 2013 Jul;6(1):220-226. Epub 2013 Apr 29.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1323](#)

AUTORES / AUTHORS: - Zhang Y; Yang H; Liu J; Deng Q; He P; Lin Y; Jiang J; Gu X; Mo M; Pan H; Xiong X; Qiu Y; He J

INSTITUCIÓN / INSTITUTION: - Southern Medical University, Guangzhou, Guangdong 510515; ; Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical College, Guangzhou, Guangdong 510120;

RESUMEN / SUMMARY: - The aim of the present study was to determine the frequency and predictive value of the expression of tumor microtubule components in patients with resected non-small cell lung cancer (R-NSCLC) subsequently treated with vinorelbine-based adjuvant chemotherapy. The expression of the microtubule components was evaluated in 85 R-NSCLC tumor samples using

immunohistochemistry. All patients received vinorelbine-based chemotherapy. The predictive value of microtubule protein expression for disease-free survival (DFS) and overall survival (OS) was assessed. The expression of the microtubule components was not associated with any baseline clinicopathological factors in the R-NSCLC patients. High tumor expression levels of class III beta-tubulin were correlated with an improved DFS ($P=0.033$) and a trend towards a longer OS ($P=0.226$). Class II and IV beta-tubulins were not correlated with patient outcome. Multivariate analysis of factors, including gender, age, histology, stage and class II, III and IV beta-tubulin expression demonstrated that high levels of class III beta-tubulin expression were correlated independently with DFS ($P=0.031$). These findings suggest that high class III beta-tubulin expression levels in resected tumors are predictive of improved DFS in R-NSCLC patients receiving vinorelbine-based chemotherapy.

[720]

TÍTULO / TITLE: - An heregulin-EGFR-HER3 autocrine signaling axis can mediate acquired lapatinib resistance in HER2+ breast cancer models.

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

REVISTA / JOURNAL: - Breast Cancer Res. 2013 Sep 18;15(5):R85.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3480](#)

AUTORES / AUTHORS: - Xia W; Petricoin EF 3rd; Zhao S; Liu L; Osada T; Cheng Q; Wulfschlegel JD; Gwin WR; Yang X; Gallagher RI; Bacus S; Lyerly HK; Spector NL

RESUMEN / SUMMARY: - INTRODUCTION: The human epidermal growth factor receptor 2 (HER2) receptor tyrosine kinase (RTK) oncogene is an attractive therapeutic target for the treatment of HER2 addicted tumors. While lapatinib, an FDA-approved small molecule HER2 and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), represents a significant therapeutic advancement in the treatment of HER2+ breast cancers, responses to lapatinib have not been durable. Consequently, elucidation of mechanisms of acquired therapeutic resistance to HER-directed therapies is of critical importance. METHODS: Using a functional protein pathway activation mapping strategy, along with targeted genomic knockdowns applied to a series of isogenic-matched pairs of lapatinib sensitive and resistant cell lines, we now report an unexpected mechanism of acquired resistance to lapatinib and other TKIs in class. RESULTS: The signaling analysis revealed that while HER2 was appropriately inhibited in lapatinib resistant cells, EGFR tyrosine phosphorylation was incompletely inhibited. Using a targeted molecular knockdown approach to interrogate the causal molecular underpinnings of EGFR persistent activation, we found that lapatinib resistant cells were no longer oncogene addicted to HER2-HER3-PI3K signaling as seen in the parental lapatinib sensitive cell lines, but instead were dependent upon an heregulin (HRG)-driven HER3-EGFR-PI3K-PDK1 signaling axis. Two FDA-approved EGFR TKIs could not overcome HRG-HER3 mediated activation of EGFR, or reverse lapatinib resistance. The ability to overcome EGFR-mediated acquired therapeutic resistance to

lapatinib was demonstrated through molecular knockdown of EGFR and treatment with the irreversible pan-HER TKI neratinib, which blocked HRG-dependent phosphorylation of HER3 and EGFR, resulting in apoptosis of resistant cells. In addition, whereas HRG reversed lapatinib-mediated antitumor effects in parental HER2+ breast cancer cells, neratinib was comparatively resistant to the effects of HRG in parental cells. Finally, we showed that HRG expression is an independent negative predictor of clinical outcome in HER2+ breast cancers, providing potential clinical relevance to our findings. CONCLUSIONS: Molecular analysis of acquired therapeutic resistance to lapatinib identified a new resistance mechanism based on incomplete and “leaky” inhibition of EGFR by lapatinib. The selective pressure applied by incomplete inhibition of the EGFR drug target resulted in selection of ligand-driven feedback that sustained EGFR activation in the face of constant exposure to the drug. Inadequate target inhibition driven by a ligand-mediated autocrine feedback loop may represent a broader mechanism of therapeutic resistance to HER TKIs and suggests adopting a different strategy for selecting more effective TKIs to advance into the clinic.

[721]

TÍTULO / TITLE: - Lower gefitinib dose led to earlier resistance acquisition before emergence of T790M mutation in EGFR mutated lung cancer model.

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

REVISTA / JOURNAL: - Cancer Sci. 2013 Sep 13. doi: 10.1111/cas.12284.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cas.12284](#)

AUTORES / AUTHORS: - Hayakawa H; Ichihara E; Ohashi K; Ninomiya T; Yasugi M; Takata S; Sakai K; Matsumoto K; Takigawa N; Tanimoto M; Kiura K

INSTITUCIÓN / INSTITUTION: - Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Hematology, Oncology, and Respiratory Medicine, Okayama, Japan.

RESUMEN / SUMMARY: - Non-small cell lung cancers (NSCLCs) with epidermal growth factor receptor (EGFR) mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs); however, unlike cytotoxic agents, it is generally accepted that minimal doses of drugs inhibiting target molecules are sufficient when molecular-targeted agents, including EGFR-TKIs, are administered. Thus, any utility of higher doses remains unclear. We compared low-dose (15 mg/kg) gefitinib therapy with high-dose (50 mg/kg) therapy using an EGFR-mutated lung cancer xenograft model. Both gefitinib doses induced tumor shrinkage, but tumors regrew in the low-dose group within 1 month, whereas tumors in the high-dose group did not. Neither the T790M mutation nor MET amplification was apparent in regrown tumors. We also compared outcomes after administration of two doses of gefitinib (5 and 25 mg/kg) in a transgenic EGFR-mutated lung cancer mouse model. In line with the results obtained using the xenograft model, both gefitinib doses completely inhibited tumor growth, but tumors

treated with the lower dose of gefitinib developed earlier drug resistance. In conclusion, administration of a low gefitinib dose caused tumors to become drug-resistant prior to acquisition of the T790M mutation or MET amplification in EGFR-mutated models of lung cancer. This suggests that it is important to optimize the EGFR-TKI dose for treatment of EGFR mutation-associated lung cancer. Gefitinib may need to be administered at a dose greater than the minimum required for inhibition of target molecules. This article is protected by copyright. All rights reserved.

[722]

TÍTULO / TITLE: - Effects of MDM2 inhibitors on vascular endothelial growth factor-mediated tumor angiogenesis in human breast cancer.

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

REVISTA / JOURNAL: - Angiogenesis. 2013 Aug 2.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10456-013-9376-3](#)

AUTORES / AUTHORS: - Xiong J; Yang Q; Li J; Zhou S

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China.

RESUMEN / SUMMARY: - BACKGROUND: Mouse double minute 2 (MDM2) is overexpressed in many malignant tumors, and MDM2 levels are associated with poor prognosis of several human cancers, including breast cancer. In the present study, we investigated the function of MDM2 in vascular endothelial growth factor (VEGF)-mediated tumor angiogenesis of breast cancer and the potential value of MDM2 as an anti-angiogenic therapy target for cancer therapy by inhibiting MDM2 with antisense oligonucleotides (ASO) or other antagonist nutlin-3. METHODS: Anti-MDM2 ASO and nutlin-3 were evaluated for their in vitro and in vivo anti-angiogenesis activities in different human breast cancer models with a different p53 status: MCF-7 cell line containing wild-type p53 and MDA-MB-468 cell line containing mutant p53. MCF-7 and MDA-MB-468 cells were incubated with different concentrations of ASO or nutlin-3 for various periods of time. VEGF gene and protein expression in tumor cells was measured by qPCR and Western blot. The level of VEGF protein secreted in the culture supernatant of treated cells was quantified by enzyme-linked immunosorbent assay (ELISA). Nude mouse xenograft models were further established to determine their effects on tumor growth and angiogenesis. Serum levels of VEGF were measured by ELISA. VEGF expression and microvessel density in tumor tissues were studied by immunohistochemistry. Both angiogenesis and tumor growth were digitally quantified. RESULTS: In both MCF-7 and MDA-MB-468 cells, VEGF expression and secretion were reduced, resulting from specific inhibition of MDM2 expression by ASO. In vivo assay, after administration of ASO, VEGF production reduced and anti-angiogenesis activity occurred in nude mice bearing MCF-7 or MDA-MB-468 xenograft. However, in both models treated with nutlin-3, VEGF production was not changed and anti-angiogenesis

activity was not observed. CONCLUSION: In summary, the ASO construct targeting MDM2 specifically suppresses VEGF expression in vitro and VEGF-mediated tumor angiogenesis in vivo in breast cancer. Furthermore, the suppression of VEGF expression subsequent to inhibition of MDM2 in p53 mutant cells suggests that MDM2 has a regulatory role on VEGF expression through a p53-independent mechanism.

[723]

TÍTULO / TITLE: - The independent, unfavorable prognostic factors endothelin A receptor and chemokine receptor 4 have a close relationship in promoting the motility of nasopharyngeal carcinoma cells via the activation of AKT and MAPK pathways.

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

REVISTA / JOURNAL: - J Transl Med. 2013 Aug 29;11(1):203.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-203](#)

AUTORES / AUTHORS: - Luo DH; Chen QY; Liu H; Xu LH; Zhang HZ; Zhang L; Tang LQ; Mo HY; Huang PY; Guo X; Mai HQ

RESUMEN / SUMMARY: - BACKGROUND: Recent studies have indicated that the expression of endothelin A receptor (ETAR) and chemokine receptor 4 (CXCR4) could be used as an indicator of the metastatic potential of nasopharyngeal carcinoma (NPC). The aim of this study was to determine the prognostic value of ETAR and CXCR4 in NPC patients and to reveal the interplay of the endothelin-1 (ET-1)/ETAR and stromal-derived factor-1(SDF-1)/CXCR4 pathways in promoting NPC cell motility. METHODS: Survival analysis was used to analyze the prognostic value of ETAR and CXCR4 expression in 153 cases of NPC. Chemotaxis assays were used to evaluate alterations in the migration ability of non-metastatic 6-10B and metastatic 5-8F NPC cells. Real-time PCR, immunoblotting, and flow cytometric analyses were used to evaluate changes in the expression levels of CXCR4 mRNA and protein induced by ET-1. RESULTS: The expression levels of ETAR and CXCR4 were closely related to each other and both correlated with a poor prognosis. A multivariate analysis showed that the expression levels of both ETAR and CXCR4 were independent prognostic factors for overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS). The migration of 6-10B and 5-8F cells was elevated by ET-1 in combination with SDF-1 α . The knockdown of ETAR protein expression by siRNA reduced CXCR4 protein expression in addition to ETAR protein expression, leading to a decrease in the metastatic potential of the 5-8F cells. ET-1 induced CXCR4 mRNA and protein expression in the 6-10B NPC cells in a time- and concentration-dependent fashion and was inhibited by an ETAR antagonist and PI3K/AKT/mTOR and MAPK/ERK1/2 pathway inhibitors. CONCLUSIONS: ETAR and CXCR4 expression levels are potential prognostic biomarkers in NPC patients. ETAR activation partially promoted NPC cell migration via a mechanism that enhanced functional CXCR4 expression.

[724]

TÍTULO / TITLE: - Quantitative T2 mapping of recurrent glioblastoma under bevacizumab improves monitoring for non-enhancing tumor progression and predicts overall survival.

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

REVISTA / JOURNAL: - Neuro Oncol. 2013 Oct;15(10):1395-404. doi: 10.1093/neuonc/not105. Epub 2013 Aug 7.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not105](#)

AUTORES / AUTHORS: - Hattingen E; Daneshvar K; Pilatus U; Mittelbronn M; Steinbach JP; Bahr O

INSTITUCIÓN / INSTITUTION: - Corresponding Author: Elke Hattingen, MD, Goethe-University Hospital Frankfurt, Schleusenweg 2-16, 60528, Frankfurt, Germany. elke.hattingen@kgu.de.

RESUMEN / SUMMARY: - Background Anti-angiogenic treatment in recurrent glioblastoma patients suppresses contrast enhancement and reduces vasogenic edema while non-enhancing tumor progression is common. Thus, the importance of T2-weighted imaging is increasing. We therefore quantified T2 relaxation times, which are the basis for the image contrast on T2-weighted images. Methods Conventional and quantitative MRI procedures were performed on 18 patients with recurrent glioblastoma before treatment with bevacizumab and every 8 weeks thereafter until further tumor progression. We segmented the tumor on conventional MRI into 3 subvolumes: enhancing tumor, non-enhancing tumor, and edema. Using coregistered quantitative maps, we followed changes in T2 relaxation time in each subvolume. Moreover, we generated differential T2 maps by a voxelwise subtraction using the first T2 map under bevacizumab as reference. Results Visually segmented areas of tumor and edema did not differ in T2 relaxation times. Non-enhancing tumor volume did not decrease after commencement of bevacizumab treatment but strikingly increased at progression. Differential T2 maps clearly showed non-enhancing tumor progression in previously normal brain. T2 relaxation times decreased under bevacizumab without re-increasing at tumor progression. A decrease of <26 ms in the enhancing tumor following exposure to bevacizumab was associated with longer overall survival. Conclusions Combining quantitative MRI and tumor segmentation improves monitoring of glioblastoma patients under bevacizumab. The degree of change in T2 relaxation time under bevacizumab may be an early response parameter predictive of overall survival. The sustained decrease in T2 relaxation times toward values of healthy tissue masks progressive tumor on conventional T2-weighted images. Therefore, quantitative T2 relaxation times may detect non-enhancing progression better than conventional T2-weighted imaging.

[725]

TÍTULO / TITLE: - Curcumin sensitizes lung adenocarcinoma cells to apoptosis via intracellular redox status mediated pathway.

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

REVISTA / JOURNAL: - Indian J Exp Biol. 2012 Dec;50(12):853-61.

AUTORES / AUTHORS: - Kaushik G; Kaushik T; Yadav SK; Sharma SK; Ranawat P; Khanduja KL; Pathak CM

INSTITUCIÓN / INSTITUTION: - Department of Biophysics, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012, India.

RESUMEN / SUMMARY: - The present study demonstrates that curcumin acts as pro-oxidant and sensitizes human lung adenocarcinoma epithelial cells (A549) to apoptosis via intracellular redox status mediated pathway. Results indicated that curcumin induced cell toxicity (light microscopy and MTT assay) and apoptosis (AnnexinV-FITC/PI labeling and caspase-3 activity) in these cells. These events seem to be mediated through generation of reactive oxygen species (ROS) and superoxide radicals (SOR) and enhanced levels of lipid peroxidation. These changes were accompanied by increase in oxidized glutathione (GSSG), reduced glutathione (GSH) and gamma-glutamylcysteine synthetase (gamma-GCS) activity, but decrease in GSH/GSSG ratio. The induction of apoptosis and decrease in GSH/GSSG ratio was also accompanied by sustained phosphorylation and activation of p38 mitogen activated protein kinase (MAPK). On the other hand, addition of N-acetyl cysteine (NAC), an antioxidant, blocked the curcumin-induced ROS production and rescued malignant cells from curcumin-induced apoptosis through caspase-3 deactivation. However, L-buthionine sulfoximine (BSO), a GSH synthesis blocking agent, further enhanced curcumin-induced ROS production and apoptosis in A549 cells. Decreased GSH/GSSG ratio seems to be a crucial factor for the activation of MAPK signaling cascade by curcumin. The study therefore, provides an insight into the molecular mechanism involved in sensitization of lung adenocarcinoma cells to apoptosis by curcumin.

[726]

TÍTULO / TITLE: - Glucocorticoid receptor-mediated apoptosis in small-cell lung cancer requires interaction with BCL-2.

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

REVISTA / JOURNAL: - Endocr Relat Cancer. 2013 Sep 13.

●● [Enlace al texto completo \(gratis o de pago\) 1530/ERC-13-0402](#)

AUTORES / AUTHORS: - Schlossmacher G; Platt E; Davies A; Meredith S; White A

INSTITUCIÓN / INSTITUTION: - G Schlossmacher, Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom.

RESUMEN / SUMMARY: - Small cell lung cancer (SCLC) tumours are highly aggressive. At time of diagnosis, patients have often developed metastases and overall prognosis is

particularly poor, making effective treatment difficult. Novel mechanisms need to be identified as treatment targets. We have previously found low levels of the glucocorticoid receptor (GR) in SCLC cell lines and demonstrated that overexpression of GR increases tumour cell death both in vitro and in vivo. We hypothesise that low levels of GR impair its inhibitory effect on BCL-2 and thus provide a survival advantage to SCLC cell lines. The mechanism behind GR-induced apoptosis is currently unknown, therefore pro- and anti-apoptotic genes were investigated for their role in GR-mediated apoptosis signalling. We found that overexpression of wild-type GR via retroviral transduction causes the DMS 79 SCLC cell line to undergo caspase-mediated apoptosis within 72 h. Neither BAD nor BIM mRNA and protein levels were affected by GR restoration implying that GR does not trigger apoptosis in the SCLC cell lines by upregulating these pro-apoptotic genes. The anti-apoptotic BCL-2 gene was significantly overexpressed in six SCLC cell lines and the BCL-2 inhibitor ABT-737 increased apoptosis in all three cell lines tested. GR interacted with BCL-2 in DMS 153, DMS 79 and COR-L42 cell lines, suggesting that a protein interaction between GR and BCL-2 could play a role in GR-induced apoptosis. A deeper understanding of the molecular mechanism for increasing GR expression in SCLC could provide novel treatment strategies in the future.

[727]

TÍTULO / TITLE: - Fractal dimension of chromatin: potential molecular diagnostic applications for cancer prognosis.

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

REVISTA / JOURNAL: - Expert Rev Mol Diagn. 2013 Sep;13(7):719-35. doi: 10.1586/14737159.2013.828889.

●● Enlace al texto completo (gratis o de pago) [1586/14737159.2013.828889](https://doi.org/10.1586/14737159.2013.828889)

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RESUMEN / SUMMARY: - Fractal characteristics of chromatin, revealed by light or electron microscopy, have been reported during the last 20 years. Fractal features can easily be estimated in digitalized microscopic images and are helpful for diagnosis and prognosis of neoplasias. During carcinogenesis and tumor progression, an increase of the fractal dimension (FD) of stained nuclei has been shown in intraepithelial lesions of the uterine cervix and the anus, oral squamous cell carcinomas or adenocarcinomas of the pancreas. Furthermore, an increased FD of chromatin is an unfavorable prognostic factor in squamous cell carcinomas of the oral cavity and the larynx, melanomas and multiple myelomas. High goodness-of-fit of the regression line of the FD is a favorable

prognostic factor in acute leukemias and multiple myelomas. The nucleus has fractal and power-law organization in several different levels, which might in part be interrelated. Some possible relations between modifications of the chromatin organization during carcinogenesis and tumor progression and an increase of the FD of stained chromatin are suggested. Furthermore, increased complexity of the chromatin structure, loss of heterochromatin and a less-perfect self-organization of the nucleus in aggressive neoplasias are discussed.

[728]

TÍTULO / TITLE: - Novel WWP2 ubiquitin ligase isoforms as potential prognostic markers and molecular targets in cancer.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Aug 9;1832(12):2127-2135. doi: 10.1016/j.bbadis.2013.08.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbadis.2013.08.001](#)

AUTORES / AUTHORS: - Soond SM; Smith PG; Wahl L; Swingler TE; Clark IM; Hemmings AM; Chantry A

INSTITUCIÓN / INSTITUTION: - School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ, UK.

RESUMEN / SUMMARY: - The WWP2 E3 ubiquitin ligase has previously been shown to regulate TGFbeta/Smad signalling activity linked to epithelial-mesenchymal transition (EMT). Whilst inhibitory I-Smad7 was found to be the preferred substrate for full-length WWP2-FL and a WWP2-C isoform, WWP2-FL also formed a stable complex with an N-terminal WWP2 isoform (WWP2-N) in the absence of TGFbeta, and rapidly stimulated activating Smad2/3 turnover. Here, using stable knockdown experiments we show that specific depletion of individual WWP2 isoforms impacts differentially on Smad protein levels, and in WWP2-N knockdown cells we unexpectedly find spontaneous expression of the EMT marker vimentin. Re-introduction of WWP2-N into WWP2-N knockout cells also repressed TGFbeta-induced vimentin expression. In support of the unique role for WWP2-N in regulating TGFbeta/Smad functional activity, we then show that a novel V717M-WWP2 mutant in the MZ7-mel melanoma cell line forms a stable complex with the WWP2-N isoform and promotes EMT by stabilizing Smad3 protein levels. Finally, we report the first analysis of WWP2 expression in cancer cDNA panel arrays using WWP2 isoform-specific probes and identify unique patterns of WWP2 isoform abundance associated with early/advanced disease stages. WWP2-N is significantly downregulated in stage IIIC melanoma and up-regulated in stage II/III prostate cancer, and we also find isolated examples of WWP2-FL and WWP2-C overexpression in early-stage breast cancer. Together, these data suggest that individual WWP2 isoforms, and particularly WWP2-N, could play central

roles in tumourigenesis linked to aberrant TGFbeta-dependent signalling function, and also have potential as both prognostic markers and molecular therapeutic targets.

[729]

- CASTELLANO -

TÍTULO / TITLE: Androgenrezeptor-Expression : Prognostische Bedeutung beim lokal fortgeschrittenen Plattenepithelkarzinom der Kopf-Hals-Region.

TÍTULO / TITLE: - Androgen receptor expression : Prognostic value in locally advanced squamous cell carcinoma of the head and neck.

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

REVISTA / JOURNAL: - Strahlenther Onkol. 2013 Aug 21.

●● Enlace al texto completo (gratis o de pago) 1007/s00066-013-0389-z

AUTORES / AUTHORS: - Rades D; Seibold ND; Schild SE; Noack F

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Lubeck, Ratzeburger Allee 160, 23538, Lubeck, Germany, rades.dirk@gmx.net.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: This study investigated the prognostic value of androgen receptor (AR) expression of tumor cells in patients treated with surgery and subsequent radio(chemo)therapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN). MATERIAL AND METHODS: The impact of AR and 11 additional factors on locoregional control (LRC), metastases-free survival (MFS), and overall survival (OS) was retrospectively studied in 163 patients with nonmetastatic stage III/IV SCCHN. Additional factors included age, gender, ECOG performance status, pre-radiotherapy (pre-RT) hemoglobin levels, tumor site, histologic grade, T category, N category, HPV status, extent of resection, and concurrent chemotherapy. RESULTS: On multivariate analysis, improved LRC was significantly associated with pre-RT hemoglobin levels ≥ 12 g/dl (risk ratio [RR] 2.22; 95 % confidence interval [CI] 1.19-4.13; $p = 0.013$), tumor site (RR 1.39; 95 % CI 1.14-1.70; $p = 0.001$), lower T category (RR 1.67; 95 % CI 1.18-2.44; $p = 0.003$), and lower N category (RR 4.18; 95 % CI 1.90-10.55; $p < 0.001$). Improved MFS was associated with AR expression (RR 2.21; 95 % CI 1.01-5.41; $p = 0.048$), better ECOG performance status (RR 3.19; 95 % CI 1.50-7.14; $p = 0.003$), lower T category (RR 2.24; 95 % CI 1.47-3.65; $p < 0.001$), and lower N category (RR 5.33; 95 % CI 2.07-16.63; $p < 0.001$). OS was positively associated with AR expression (RR 1.99; 95 % CI 1.06-4.00; $p = 0.032$), better ECOG performance status (RR 2.20; 95 % CI 1.20-4.09; $p = 0.010$), pre-RT hemoglobin levels ≥ 12 g/dl (RR 2.13; 95 % CI 1.19-3.82; $p = 0.012$), lower T category (RR 1.81; 95 % CI 1.30-2.62; $p < 0.001$), and lower N category (RR 3.41; 95 % CI: 1.65-7.80; $p < 0.001$). CONCLUSION: Tumor cell expression of AR was an independent prognostic factor for MFS and OS and should be considered in future prospective trials.

[730]

TÍTULO / TITLE: - Case report: clearance to dive for a naval candidate with family history of malignant hyperthermia.

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

REVISTA / JOURNAL: - Undersea Hyperb Med. 2013 Jul-Aug;40(4):365-9.

AUTORES / AUTHORS: - Vigilante JA

INSTITUCIÓN / INSTITUTION: - Division of Undersea Medicine, Captain James A. Lovell Federal Health Care Center, Great Lakes, Illinois, USA. john.vigilante@med.navy.mil

RESUMEN / SUMMARY: - INTRODUCTION: A 20-year-old male military recruit who presented for a screening physical for U.S.Naval Diving Duty was found to have family history significant for malignant hyperthermia. He had never been exposed to anesthesia, a trigger for the condition, and had not undergone testing. Medical history was otherwise unremarkable, and the patient was cleared for diving. METHODS: Literature search was conducted using PubMed/Medline. Keywords included malignant hyperthermia, exertional heat illness, exertional rhabdomyolysis, diving, special operations, military. Results that included cases of malignant hyperthermia were included. RESULTS: Review of the literature reveals that malignant hyperthermia is primary a pharmacogenetic disorder limited to specific anesthetics, with rare reports of environmental triggers. Analysis of the disease, as well as the absence of reported cases of malignant hyperthermia in diving, suggest there is minimal increased risk in diving for subjects without history of exercise intolerance. CONCLUSION: Individuals with presumed or proven malignant hyperthermia susceptibility seeking activity clearance should be given precautions and undergo careful questioning for history of heat- or exercise-related illness. If negative, it seems reasonable to allow the patient participation in recreational or technical diving.

[731]

TÍTULO / TITLE: - Association of CYP3A4/5, ABCB1 and ABCC2 polymorphisms and clinical outcomes of Thai breast cancer patients treated with tamoxifen.

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

REVISTA / JOURNAL: - Pharmgenomics Pers Med. 2013 Aug 26;6:93-8. doi: 10.2147/PGPM.S44006.

●● Enlace al texto completo (gratis o de pago) [2147/PGPM.S44006](#)

AUTORES / AUTHORS: - Sensorn I; Sirachainan E; Chamnanphon M; Pasomsub E; Trachu N; Supavilai P; Sukasem C; Pinthong D

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand.

RESUMEN / SUMMARY: - BACKGROUND: Pharmacogenetic study of cytochrome P450 (CYP) gene CYP2D6 and tamoxifen outcomes remain controversial. Apart from CYP2D6, other drug-metabolizing enzymes and transporters also play a role in tamoxifen

metabolic pathways. The aim of this study is to investigate the impact of CYP3A4/5, ABCB1, and ABCC2 polymorphisms on the risk of recurrence in Thai patients who received tamoxifen adjuvant therapy. METHODS: Patients with early-stage breast cancer who received tamoxifen adjuvant therapy were recruited in this study. All six single-nucleotide polymorphisms (SNPs), including CYP3A4*1B (-392 A>G)/*18(878 T>C), CYP3A5*3(6986 G>A), ABCB1 3435 C>T, ABCC2*1C(-24 C>T), and ABCC2 68231 A>G, were genotyped using real-time polymerase chain reaction assays. The impacts of genetic variants on disease-free survival (DFS) were analyzed using the Kaplan-Meier method and Cox regression analysis. RESULTS: The ABCB1 3435 C>T was found to have the highest allele frequency among other variants; however, CYP3A4*1B/*18 could not be found in this study. Patients with heterozygous ABCB1 3435 CT genotype showed significantly shorter DFS than those with homozygous 3435 CC genotype (P = 0.041). In contrast, patients who carried homozygous 3435 TT genotype showed no difference in DFS from wild-type 3435 CC patients. Cox regression analysis showed that the relative risk of recurrence was increased by five times (P = 0.043; hazard ratio = 5.11; 95% confidence interval: 1.05-24.74) in those patients carrying ABCB1 3435 CT genotype compared to those with ABCB1 3435 CC. CONCLUSION: ABCB1 3435 C>T is likely to have a clinically significant impact on recurrence risk in Thai patients with breast cancer who receive tamoxifen adjuvant therapy.

[732]

TÍTULO / TITLE: - The role of glycogen synthase kinase-3beta in glioma cell apoptosis induced by remifentanyl.

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

REVISTA / JOURNAL: - Cell Mol Biol Lett. 2013 Aug 29.

●● [Enlace al texto completo \(gratis o de pago\) 2478/s11658-013-0102-3](#)

AUTORES / AUTHORS: - Xu J; Xu P; Li Z; Xiao L; Yang Z

INSTITUCIÓN / INSTITUTION: - College of Medicine, Nankai University, Tianjin, 300071, China.

RESUMEN / SUMMARY: - The aim of malignant glioma treatment is to inhibit tumor cell proliferation and induce tumor cell apoptosis. Remifentanyl is a clinical anesthetic drug that can activate the N-methyl-D-aspartate (NMDA) receptor. NMDA receptor signaling activates glycogen synthase kinase-3beta (GSK-3beta). Discovered some 32 years ago, GSK-3beta was only recently considered as a therapeutic target in cancer treatment. The purpose of this study was to assess whether remifentanyl can induce the apoptosis of C6 cells through GSK-3beta activation. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used to detect cell viability. Hoechst 33342 staining and flow cytometry were used to detect cell apoptosis. The effect of GSK-3beta activation was detected using a GSK-3beta activation assay kit and 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (TDZD-8), a potent and selective small molecule inhibitor of GSK-3beta. The MTT assay indicated that remifentanyl induced C6 cell

death in a concentration- and time-dependent manner. Hoechst 33342 staining and flow cytometry showed that remifentanil significantly induced C6 cell apoptosis. The measurement of GSK-3beta activation showed that remifentanil increased the cellular level of GSK-3beta. All of these toxic effects can be attenuated by treatment with TDZD-8. These results suggest that remifentanil is able to induce C6 cell apoptosis through GSK-3beta activation, which provides a basis for its potential use in the treatment of malignant gliomas.

[733]

TÍTULO / TITLE: - Molecular Dynamic Simulation: A Powerful Method for Prediction of Apoptotic Pore Formation.

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

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1007/s12013-013-9747-9](#)

AUTORES / AUTHORS: - Poursadegh Zonouzi A; Arzani Zonoz N; Ghorbian S

INSTITUCIÓN / INSTITUTION: - Department of Cellular and Molecular Biology, Faculty of Science, Azarbaijan Shahid Madani University, Tabriz, Iran.

[734]

TÍTULO / TITLE: - DNA methyltransferase inhibitor-mediated apoptosis in the Wnt/beta-catenin signal pathway in a renal cell carcinoma cell line.

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

REVISTA / JOURNAL: - Exp Biol Med (Maywood). 2013 Sep 1;238(9):1009-16. doi: 10.1177/1535370213498984. Epub 2013 Aug 23.

●● Enlace al texto completo (gratis o de pago) [1177/1535370213498984](#)

AUTORES / AUTHORS: - Konac E; Varol N; Yilmaz A; Menevse S; Sozen S

INSTITUCIÓN / INSTITUTION: - Department of Medical Biology and Genetics, Faculty of Medicine, Gazi University, Besevler, 06500, Ankara, Turkey.

RESUMEN / SUMMARY: - The Wnt signaling pathway is activated in most cancer types when Wnt antagonist genes are inactivated. Glycogen synthase kinase 3 (GSK3beta) is an important regulator of the Wnt/beta-catenin signaling pathway. The mechanisms underlying GSK3beta regulation of neoplastic transformation and tumor development are unclear. Studies have raised the possibility that the Wnt signaling pathway may be implicated in renal cell carcinoma (RCC). Therefore, in the present study, we hypothesize that the expression and methylation status of the secreted frizzled-related protein 2 (sFRP2) gene, one of the secreted antagonists that bind Wnt protein, and re-expression of this gene with the demethylation agent (5-aza-2'-deoxycytidine; DAC) may induce apoptosis in RCC cells. To test this hypothesis, we investigated the relationship among epigenetic inactivation of sFRP2 and p-GSK3beta (Ser9) and other

Wnt antagonists (sFRP1, DKK3, WIF-1) and apoptotic factors (Bax and Caspase3) as well as the anti-apoptotic factor BCL2. Our results indicate that DAC-mediated inhibition of DNA methylation led to a re-activation of sFRP2 expression and increased expression levels of the Wnt antagonists and apoptotic factors. In contrast, the level of beta-catenin (CTNNB1) expression decreased. The p-GSK3beta (Ser9) protein level in Caki-2 cells was significantly down-regulated, while the DNA fragmentation rate increased after treatment with 5 muM DAC at 96 h. Our data show that sFRP2 functions as a tumor suppressor gene in RCC and that its restoration may offer a new therapeutic approach for the treatment of RCC. Moreover, our study draws attention to the regulatory features of epigenetic molecules and analyses their underlying molecular mechanisms of action and their potential use in clinical practice.

[735]

TÍTULO / TITLE: - Histone acetyltransferase PCAF Up-regulated cell apoptosis in hepatocellular carcinoma via acetylating histone H4 and inactivating AKT signaling.

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

REVISTA / JOURNAL: - Mol Cancer. 2013 Aug 27;12(1):96.

●● Enlace al texto completo (gratis o de pago) [1186/1476-4598-12-96](#)

AUTORES / AUTHORS: - Zheng X; Gai X; Ding F; Lu Z; Tu K; Yao Y; Liu Q

RESUMEN / SUMMARY: - BACKGROUND: PCAF is an important intrinsic histone acetyltransferases. This study tried to establish the effect of PCAF on HCC cell apoptosis. METHOD: Both in vitro and in vivo experiments including IHC, DAPI staining, caspase3/7 activity assay, BrdU assay, MTT assay, western immunoblotting and co-immunoprecipitation were used here. RESULTS: PCAF was found to be expressed at the low level in most of HCC cell lines. PCAF overexpression induced cell apoptosis and growth arrest with increased Histone H4 acetylation and inactivation of AKT signaling in Huh7 and HepG2 cells. The opposite results were obtained by silencing PCAF in Hep3B cells. The co-immunoprecipitation assay confirmed that PCAF protein was bound with histone H4 protein in the nucleus of Hep3B cells. Finally, the in vivo experiment confirmed the findings mentioned-above. CONCLUSION: These data identified PCAF promotes cell apoptosis and functions as a HCC repressor through acetylating histone H4 and inactivating AKT signaling.

[736]

TÍTULO / TITLE: - Preclinical evaluation of BAY 1075553, a novel F-labelled inhibitor of prostate-specific membrane antigen for PET imaging of prostate cancer.

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

REVISTA / JOURNAL: - Eur J Nucl Med Mol Imaging. 2013 Aug 17.

●● Enlace al texto completo (gratis o de pago) [1007/s00259-013-2527-3](#)

AUTORES / AUTHORS: - Lesche R; Kettschau G; Gromov AV; Bohnke N; Borkowski S; Monning U; Hegele-Hartung C; Dohr O; Dinkelborg LM; Graham K

INSTITUCIÓN / INSTITUTION: - Global Drug Discovery, Bayer Healthcare, Berlin, Germany, Muellerstrasse 178, 13342, Berlin, Germany, ralf.lesche@bayer.com.

RESUMEN / SUMMARY: - **PURPOSE:** Prostate-specific membrane antigen (PSMA) is a transmembrane protein overexpressed in prostate cancer and is therefore being explored as a biomarker for diagnosing and staging of the disease. Here we report preclinical data on BAY 1075553 (a 9:1 mixture of (2S,4S)- and (2R,4S)-2-[¹⁸F]fluoro-4-phosphonomethyl-pentanedioic acid), a novel ¹⁸F-labelled small molecule inhibitor of PSMA enzymatic activity, which can be efficiently synthesized from a direct radiolabelling precursor. **METHODS:** The ¹⁸F-radiolabelled stereoisomers of 2-[¹⁸F]fluoro-4-(phosphonomethyl)-pentanedioic acid were synthesized from their respective isomerically pure precursors dimethyl 2-[[bis(benzyloxy)phosphoryl]methyl]-4-(tosyloxy)pentanedioate. In vivo positron emission tomography (PET) imaging and biodistribution studies were conducted in mice bearing LNCaP, 22Rv1 and PC-3 tumours. Pharmacokinetic parameters and dosimetry estimates were calculated based on biodistribution studies in rodents. For non-clinical safety assessment (safety pharmacology, toxicology) to support a single-dose human microdose study, off-target effects in vitro, effects on vital organ functions (cardiovascular in dogs, nervous system in rats), mutagenicity screens and an extended single-dose study in rats were conducted with the non-radioactive racemic analogue of BAY 1075553. **RESULTS:** BAY 1075553 showed high tumour accumulation specific to PSMA-positive tumour-bearing mice and was superior to other stereoisomers tested. Fast clearance of BAY 1075553 resulted overall in low background signals in other organs except for high uptake into kidney and bladder which was mainly caused by renal elimination of BAY 1075553. A modest uptake into bone was observed which decreased over time indicating organ-specific uptake as opposed to defluorination of BAY 1075553 in vivo. Biodistribution studies found highest organ doses for kidneys and the urinary bladder wall resulting in a projected effective dose (ED) in humans of 0.0219 mSv/MBq. Non-clinical safety studies did not show off-target activity, effects on vital organs function or dose-dependent adverse effects. **CONCLUSION:** BAY 1075553 was identified as a promising PET tracer for PSMA-positive prostate tumours in preclinical studies. BAY 1075553 can be produced using a robust, direct radiosynthesis procedure. Pharmacokinetic, toxicology and safety pharmacology studies support the application of BAY 1075553 in a first-in-man microdose study with single i.v. administration.

[737]

TÍTULO / TITLE: - MicroRNAs induced in melanoma treated with combination targeted therapy of Temsirolimus and Bevacizumab.

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

REVISTA / JOURNAL: - J Transl Med. 2013 Sep 18;11(1):218.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-5876-11-218](#)

AUTORES / AUTHORS: - Wagenseller AG; Shada A; D Auria KM; Murphy C; Sun D; Molhoek KR; Papin JA; Dutta A; Slingluff CL Jr

RESUMEN / SUMMARY: - **BACKGROUND:** Targeted therapies directed at commonly overexpressed pathways in melanoma have clinical activity in numerous trials. Little is known about how these therapies influence microRNA (miRNA) expression, particularly with combination regimens. Knowledge of miRNAs altered with treatment may contribute to understanding mechanisms of therapeutic effects, as well as mechanisms of tumor escape from therapy. We analyzed miRNA expression in metastatic melanoma tissue samples treated with a novel combination regimen of Temsirolimus and Bevacizumab. Given the preliminary clinical activity observed with this combination regimen, we hypothesized that we would see significant changes in miRNA expression with combination treatment. **METHODS:** Using microarray analysis we analyzed miRNA expression levels in melanoma samples from a Cancer Therapy Evaluation Program-sponsored phase II trial of combination Temsirolimus and Bevacizumab in advanced melanoma, which elicited clinical benefit in a subset of patients. Pre-treatment and post-treatment miRNA levels were compared using paired t-tests between sample groups (patients), using a p-value < 0.01 for significance. **RESULTS:** microRNA expression remained unchanged with Temsirolimus alone; however, expression of 15 microRNAs was significantly upregulated (1.4 to 2.5-fold) with combination treatment, compared to pre-treatment levels. Interestingly, twelve of these fifteen miRNAs possess tumor suppressor capabilities. We identified 15 putative oncogenes as potential targets of the 12 tumor suppressor miRNAs, based on published experimental evidence. For 15 of 25 miRNA-target mRNA pairings, changes in gene expression from pre-treatment to post-combination treatment samples were inversely correlated with changes in miRNA expression, supporting a functional effect of those miRNA changes. Clustering analyses based on selected miRNAs suggest preliminary signatures characteristic of clinical response to combination treatment and of tumor BRAF mutational status. **CONCLUSIONS:** To our knowledge, this is the first study analyzing miRNA expression in pre-treatment and post-treatment human metastatic melanoma tissue samples. This preliminary investigation suggests miRNAs that may be involved in the mechanism of action of combination Temsirolimus and Bevacizumab in metastatic melanoma, possibly through inhibition of oncogenic pathways, and provides the preliminary basis for further functional studies of these miRNAs.

TÍTULO / TITLE: - The Prognostic Significance of the Biomarker p16 in Oropharyngeal Squamous Cell Carcinoma.

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

REVISTA / JOURNAL: - Clin Oncol (R Coll Radiol). 2013 Jul 31. pii: S0936-6555(13)00273-2. doi: 10.1016/j.clon.2013.07.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.clon.2013.07.003](#)

AUTORES / AUTHORS: - Oguejiofor KK; Hall JS; Mani N; Douglas C; Slevin NJ; Homer J; Hall G; West CM

INSTITUCIÓN / INSTITUTION: - Translational Radiobiology Group, Institute of Cancer Sciences, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK.

RESUMEN / SUMMARY: - AIMS: There is an increasing incidence of human papillomavirus (HPV)-positive oropharyngeal squamous cell cancers (OPSCC) mostly associated with favourable outcomes. p16 immunohistochemistry is a surrogate marker for HPV positivity in OPSCC. The prognostic strength of p16 over traditional prognostic factors is not fully characterised. In this study, we evaluated the clinical and demographic differences between p16-positive and -negative OPSCC and characterised its prognostic strength versus traditional prognostic factors. MATERIALS AND METHODS: Formalin-fixed, paraffin-embedded blocks and clinical information from 217 OPSCC patients, treated with radiotherapy (alone or in combination with other therapies) between 2000 and 2010 were collected retrospectively. Immunohistochemistry for p16 protein was carried out; cancer-specific survival (CSS), recurrence-free survival (RFS) and locoregional control (LRC) were calculated for both univariate and multivariate analyses. RESULTS: Ninety-two per cent of the OPSCC originated from tonsil and tongue base sites, 61% were p16 positive. Patients with p16-positive OPSCC were younger ($P < 0.0001$), with lower alcohol ($P = 0.0002$) and tobacco ($P = 0.0001$) exposure. The tumours were less differentiated ($P = 0.0069$), had a lower T stage ($P = 0.0027$), higher nodal status ($P = 0.014$) and higher American Joint Committee on Cancer (AJCC) prognostic group ($P = 0.0036$). AJCC prognostic group was significant for RFS ($P = 0.0096$) and CSS ($P = 0.018$) in patients with p16-negative OPSCC, but not those with p16-positive tumours ($P = 0.30$ and 0.54). Other significant factors for CSS and RFS in univariate analysis were: pretreatment haemoglobin ($P < 0.0001$ and < 0.0001), chemoradiotherapy ($P = 0.005$ and 0.03) and P16 status ($P < 0.0001$ and 0.0001). In multivariate analysis, p16 positivity was the strongest independent prognostic variable for both CSS, RFS and LRC ($P < 0.0001$, hazard ratio 4.15; 95% confidence interval 2.43-7.08), ($P < 0.0001$, hazard ratio 6.15; 95% confidence interval 3.57-10.61) and ($P = 0.001$, hazard ratio 3.74; confidence interval 1.76-7.95). CONCLUSION: This study shows that p16 is the single most important prognostic variable in OPSCC, surpassing traditional prognostic factors for both CSS and RFS. Furthermore, disease stage has no prognostic significance in p16-positive patients, highlighting the need for routine p16 assessment in OPSCC.

[739]

TÍTULO / TITLE: - Cystatin C and lactoferrin concentrations in biological fluids as possible prognostic factors in eye tumor development.

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

REVISTA / JOURNAL: - Int J Circumpolar Health. 2013 Aug 5;72. doi: 10.3402/ijch.v72i0.21087.

●● Enlace al texto completo (gratis o de pago) [3402/ijch.v72i0.21087](#)

AUTORES / AUTHORS: - Dikovskaya MA; Trunov AN; Chernykh VV; Korolenko TA

INSTITUCIÓN / INSTITUTION: - Institute of Physiology, Siberian Branch of Russian Academy of Medical Sciences, Novosibirsk, Russia ; The S.N. Fyodorov Federal State Complex "Eye Microsurgery" (Novosibirsk Branch), Novosibirsk, Russia.

RESUMEN / SUMMARY: - **OBJECTIVES:** To investigate the possible role of cystatin C in eye biological fluids locally and in serum and lactoferrin revealing anti-tumor activity in eye tumor development. **BACKGROUND:** The increased number of eye tumors was registered recently not only in the countries with high insolation, but also in the northern countries including Russia (11 cases per million of population). Search for new biological markers is important for diagnosis and prognosis in eye tumors. Cystatin C, an endogenous inhibitor of cysteine proteases, plays an important protective role in several tumors. Lactoferrin was shown to express anti-tumor and antiviral activities. It was hypothesized that cystatin C and lactoferrin could serve as possible biomarkers in the diagnosis of malignant and benign eye tumors. **STUDY DESIGN:** A total of 54 patients with choroidal melanoma and benign eye tumors were examined (part of them undergoing surgical treatment). Serum, tear fluid and intraocular fluid samples obtained from the anterior chamber of eyes in patients with choroidal melanoma were studied. **METHODS:** Cystatin C concentration in serum and eye biological fluids was measured by commercial ELISA kits for human (BioVendor, Czechia); lactoferrin concentration - by Lactoferrin-strip D 4106 ELISA test systems (Vector-BEST, Novosibirsk Region, Russia). **RESULTS:** Cystatin C concentration in serum of healthy persons was significantly higher as compared to tear and intraocular fluids. In patients with choroidal melanoma, increased cystatin C concentration was similar in tear fluid of both the eyes. Lactoferrin level in tear fluid of healthy persons was significantly higher than its serum level. Significantly increased lactoferrin concentration in tear fluid was noted in patients with benign and malignant eye tumors. **CONCLUSION:** Increased level of cystatin C in tear fluid seems to be a possible diagnostic factor in the eye tumors studied. However, it does not allow us to differentiate between malignant and benign eye tumors. Similar changes were noted for lactoferrin in tear fluid.

[740]

TÍTULO / TITLE: - Epidermal growth factor receptor exon 20 mutation increased in post-chemotherapy patients with non-small cell lung cancer detected with patients' blood samples.

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

REVISTA / JOURNAL: - Transl Oncol. 2013 Aug 1;6(4):504-10. Print 2013 Aug.

AUTORES / AUTHORS: - Wang Y; Bao W; Shi H; Jiang C; Zhang Y

INSTITUCIÓN / INSTITUTION: - Department of Basic Medical Science, Zhejiang Chinese Medical University. Hangzhou, China.

RESUMEN / SUMMARY: - **PURPOSE:** Patients with non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR)-mutations have excellent response to EGFR tyrosine kinase inhibitors (TKIs), and exon 20 mutation accounts for most of TKI drug resistance. Nested polymerase chain reaction (PCR) was used to detect EGFR exon 20 mutations of patients with NSCLC after chemotherapy. The same is being analyzed with patients' characteristics. **METHODS:** Peripheral blood samples were collected from 273 patients with NSCLC, including 143 with adenocarcinoma (ADC) and 130 with squamous cell carcinoma (SCC), after chemotherapy. DNA was extracted from whole blood for nested PCR amplification and purification. Sequencing was carried out in an automated 3730 sequencer, followed by analysis of EGFR exon 20 mutations from nested PCR products. **RESULTS:** The mutations of EGFR exon 20 were mainly point mutations in rs1050171 (c.2361^a>G) and rs56183713 (c.2457G>A). The point mutation was 28.21%, 28.46%, and 27.97% in patients with NSCLC, ADC and SCC, respectively. Men had an equivalent mutation (27.18%) to women (30.77%). The mutation in smokers and nonsmokers was 27.68% and 29.17%, respectively. In unselected patients, there was no correlation between EGFR exon 20 mutations and patients' characteristics of age, gender, smoking history, histologic type, or tumor-node-metastasis (TNM) staging system. In subgroup analyses, the EGFR mutation of patients with SCC was correlated with TNM stage [P = .013; odds ratio = 1.758; 95% confidence interval (CI) = 1.125-2.747]. **CONCLUSIONS:** The data indicate that the chemotherapy may induce EGFR-TKI-resistant mutation in NSCLC cells and EGFR-TKI should be used in the early stage of NSCLC but not after chemotherapy.

[741]

TÍTULO / TITLE: - Novel Inhibitors of Cyclin-Dependent Kinases Combat Hepatocellular Carcinoma without Inducing Chemoresistance.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

●● [Enlace al texto completo \(gratis o de pago\) 1158/1535-7163.MCT-13-](#)

[0263](#)

AUTORES / AUTHORS: - Haider C; Grubinger M; Reznickova E; Weiss TS; Rotheneder H; Miklos W; Berger W; Jorda R; Zatloukal M; Gucky T; Strnad M; Krystof V; Mikulits W

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Department of Medicine I, Institute of Cancer Research, Comprehensive Cancer Center Vienna; 2Max F. Perutz Laboratories, Department of Medical Biochemistry, Medical University of Vienna, Vienna, Austria; 3Laboratory of Growth Regulators, Faculty of Science, Palacky University & Institute of Experimental Botany; 4Centre of the Region Hana for Biotechnological and Agricultural Research, Department of Growth Regulators, Palacky University, Olomouc, Czech Republic; and 5Department of Pediatrics and Juvenile Medicine, Center for Liver Cell Research, University Hospital Regensburg, Regensburg, Germany.

RESUMEN / SUMMARY: - Treatment options for hepatocellular carcinoma using chemotherapeutics at intermediate and advanced stages of disease are limited as patients most rapidly escape from therapy and succumb to disease progression. Mechanisms of the hepatic xenobiotic metabolism are mostly involved in providing chemoresistance to therapeutic compounds. Given the fact that the aberrant activation of cyclin-dependent kinases (CDK) is frequently observed in hepatocellular carcinomas, we focused on the efficacy of the novel compounds BA-12 and BP-14 that antagonize CDK1/2/5/7 and CDK9. Inhibition of those CDKs in human hepatocellular carcinoma cell lines reduced the clonogenicity by arresting cells in S-G2 and G2-M phase of the cell cycle and inducing apoptosis. In contrast, primary human hepatocytes failed to show cytotoxicity and apoptosis. No loss of chemosensitivity was observed in hepatocellular carcinoma cells after long-term exposure to inhibitors. In vivo, treatment of xenografted human hepatocellular carcinomas with BA-12 or BP-14 effectively repressed tumor formation. Moreover, BA-12 or BP-14 significantly diminished diethylnitrosamine (DEN)-induced hepatoma development in mice. These data show that BA-12 or BP-14 exhibit strong antitumorigenic effects in the absence of chemoresistance, resulting in a superior efficacy compared with currently used chemotherapeutics in hepatocellular carcinomas. Mol Cancer Ther; 12(10); 1-11. ©2013 AACR.

[742]

TÍTULO / TITLE: - A model of sensitivity and resistance to histone deacetylase inhibitors in diffuse large B cell lymphoma: Role of cyclin-dependent kinase inhibitors.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 2;14(10).

AUTORES / AUTHORS: - Tula-Sanchez AA; Havas AP; Alonge PJ; Klein ME; Doctor SR; Pinkston W; Glinsmann-Gibson BJ; Rimsza LM; Smith CL

INSTITUCIÓN / INSTITUTION: - Dept. of Pharmacology and Toxicology; College of Pharmacy; University of Arizona; Tucson, AZ USA.

RESUMEN / SUMMARY: - Diffuse large B cell lymphoma (DLBCL) is an aggressive form of non-Hodgkin lymphoma. While the initial treatment strategy is highly effective, relapse

occurs in 40% of cases. Histone deacetylase inhibitors (HDACi) are a promising class of anti-cancer drugs but their single agent efficacy against relapsed DLBCL has been variable, ranging from few complete/partial responses to some stable disease. However, most patients showed no response to HDACi monotherapy for unknown reasons. Here we show that sensitivity and resistance to the hydroxamate HDACi, PXD101, can be modeled in DLBCL cell lines. Sensitivity is characterized by G 2/M arrest and apoptosis and resistance by reversible G 1 growth arrest. These responses to PXD101 are independent of several negative prognostic indicators such as DLBCL subtype, BCL2 and MYC co-expression, and p53 mutation, suggesting that HDACi might be used effectively against highly aggressive DLBCL tumors if they are combined with other therapeutics that overcome HDACi resistance. Our investigation of mechanisms underlying HDACi resistance showed that cyclin-dependent kinase inhibitors (CKIs), p21 and p27, are upregulated by PXD101 in a sustained fashion in resistant cell lines concomitant with decreased activity of the cyclin E/cdk2 complex and decreased Rb phosphorylation. PXD101 treatment results in increased association of CKI with the cyclin E/cdk2 complex in resistant cell lines but not in a sensitive line, indicating that the CKIs play a key role in G 1 arrest. The results suggest several treatment strategies that might increase the efficacy of HDACi against aggressive DLBCL.

[743]

TÍTULO / TITLE: - Inhibiting signal transducer and activator of transcription-3 increases response to gemcitabine and delays progression of pancreatic cancer.

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

REVISTA / JOURNAL: - Mol Cancer. 2013 Sep 11;12(1):104.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-104](#)

AUTORES / AUTHORS: - Venkatasubbarao K; Peterson L; Zhao S; Hill P; Cao L; Zhou Q; Nawrocki ST; Freeman JW

RESUMEN / SUMMARY: - BACKGROUND: Among the solid tumors, human pancreatic ductal adenocarcinoma (PDAC) has the worst prognosis. Gemcitabine is the standard first line of therapy for pancreatic cancer but has limited efficacy due to inherent or rapid development of resistance and combining EGFR inhibitors with this regimen results in only a modest clinical benefit. The goal of this study was to identify molecular targets that are activated during gemcitabine therapy alone or in combination with an EGFR inhibitor. METHODS: PDAC cell lines were used to determine molecular changes and rates of growth after treatment with gemcitabine or an EGFR inhibitor, AG1478, by Western blot analysis and MTT assays respectively. Flow cytometric analysis was performed to study the cell cycle progression and rate of apoptosis after gemcitabine treatment. ShRNA was used to knockdown STAT3. An in vivo orthotopic animal model was used to evaluate STAT3 as a target.

Immunohistochemical analysis was performed to analyze Ki67 and STAT3 expression in

tumors. RESULTS: Treatment with gemcitabine increased the levels of EGFR^{Tyr1068} and ERK phosphorylation in the PDAC cell lines tested. The constitutive STAT3^{Tyr705} phosphorylation observed in PDAC cell lines was not altered by treatment with gemcitabine. Treatment of cells with gemcitabine or AG1478 resulted in differential rate of growth inhibition. AG1478 efficiently blocked the phosphorylation of EGFR^{Tyr1068} and inhibited the phosphorylation of down-stream effectors AKT and ERKs, while STAT3^{Tyr705} phosphorylation remained unchanged. Combining these two agents neither induced synergistic growth suppression nor inhibited STAT3^{Tyr705} phosphorylation, thus prompting further studies to assess whether targeting STAT3 improves the response to gemcitabine or AG1478. Indeed, knockdown of STAT3 increased sensitivity to gemcitabine by inducing pro-apoptotic signals and by increasing G1 cell cycle arrest. However, knockdown of STAT3 did not enhance the growth inhibitory potential of AG1478. In vivo orthotopic animal model results show that knockdown of STAT3 caused a significant reduction in tumor burden and delayed tumor progression with increased response to gemcitabine associated with a decrease in the Ki-67 positive cells. CONCLUSIONS: This study suggests that STAT3 should be considered an important molecular target for therapy of PDAC for enhancing the response to gemcitabine.

[744]

TÍTULO / TITLE: - Induction of tumor cell apoptosis by a proteasome deubiquitinase inhibitor is associated with oxidative stress.

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

REVISTA / JOURNAL: - Antioxid Redox Signal. 2013 Sep 7.

●● [Enlace al texto completo \(gratis o de pago\) 1089/ars.2013.5322](#)

AUTORES / AUTHORS: - Brnjic S; Mazurkiewicz M; Fryknas M; Sun C; Zhang X; Larsson R; D'Arcy P; Linder ST

INSTITUCIÓN / INSTITUTION: - Karolinska Institute, Oncology-Pathology, Stockholm, Sweden ; Slavica.Brnjic@ki.se.

RESUMEN / SUMMARY: - Aims: b-AP15 is a recently described small molecular weight inhibitor of the USP14/UCHL5 deubiquitinases of the 19S proteasome. Inhibition of proteasome function by b-AP15 leads to an apoptotic response which, in contrast to the clinically used proteasome inhibitor bortezomib, is insensitive to Bcl-2 overexpression. The aim of the present study was to characterize the cellular response to the b-AP15 deubiquitinase inhibitor. Results: We report that b-AP15 elicits an enhanced induction of oxidative stress and rapid activation of JNK/AP-1 signaling. Pharmacological inhibition of JNK and scavenging of reactive oxygen species reduced b-AP15-induced apoptosis. We further report that ER stress is induced by b-AP15 and is involved in apoptosis induction. In contrast to bortezomib, ER stress is associated with induction of eIF2- α phosphorylation. Innovation: The findings establish that

different modes of proteasome inhibition may result in distinct cellular responses.
Conclusion: Our data suggest that an important underlying mechanism for the rapid and strong apoptotic response to b-AP15 is the induction of enhanced oxidative stress.

[745]

TÍTULO / TITLE: - Reactive oxygen species, apoptosis and cancer.

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

REVISTA / JOURNAL: - Vojnosanit Pregl. 2013 Jul;70(7):675-8.

AUTORES / AUTHORS: - Stojnev S; Ristic-Petrovic A; Jankovic-Velickovic L

INSTITUCIÓN / INSTITUTION: - Faculty of Medicine, University of Nis, Nis, Serbia.

slavicastojnev@gmail.com

[746]

TÍTULO / TITLE: - Unveiling the paradoxical nature of myelodysplastic syndromes (MDS): Why hypercellular marrow strongly favors accelerated apoptosis.

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

REVISTA / JOURNAL: - Biochem Cell Biol. 2013 Oct;91(5):303-8. doi: 10.1139/bcb-2012-0109. Epub 2013 Mar 21.

●● [Enlace al texto completo \(gratis o de pago\) 1139/bcb-2012-0109](#)

AUTORES / AUTHORS: - Das M; Chaudhuri S; Law S

INSTITUCIÓN / INSTITUTION: - a Stem Cell Research and Application Unit, Department of Biochemistry and Medical Biotechnology, Calcutta School of Tropical Medicine, 108 C R Avenue, Kolkata, West Bengal, India, 700073.

RESUMEN / SUMMARY: - The pathogenesis of bone marrow failure in myelodysplastic syndromes (MDS) is an unresolved mystery. MDS causes peripheral blood cytopenias and increased bone marrow cellularity. This apparent paradox has been interpreted as a sign of intramedullary destruction of a substantial portion of the developing hematopoietic cells by apoptosis. The present study aimed to delineate the exact mechanistic relationship between the bone marrow hypercellularity and the accelerated apoptosis in an N-ethyl-N-nitrosourea (ENU)-induced experimental MDS mouse model. The observations made so far clarify the quantitative and qualitative changes that occur in the bone marrow microenvironment through cell cycle analysis, especially involving the telomerase reverse transcriptase (TERT) and p53 expression patterns. The survival fate of the bone marrow cells were observed by measuring the expression level of some intracellular protein molecules like apoptosis signal-regulating kinase 1 (ASK-1), c-Jun N-terminal kinase (JNK), and cleaved caspase-3 of the extrinsic pathway toward apoptosis. We found myelodysplasia damage occurs within one or more multipotent progenitor populations resulting in uncontrolled cellular proliferation within the MDS bone marrow. Then, due to homeostatic balance, this

high cellular burden is minimized by activating the apoptosis pathway. As a result, the peripheral blood suffers cellular deprivation. This study can throw some light on the mechanism of disease progression and also help to reveal the paradoxical nature of the disease.

[747]

TÍTULO / TITLE: - Substituted 2-hydroxy-N-(arylalkyl)benzamides induce apoptosis in cancer cell lines.

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

REVISTA / JOURNAL: - Eur J Med Chem. 2013 Aug 14;68C:253-259. doi: 10.1016/j.ejmech.2013.08.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.08.009](https://doi.org/10.1016/j.ejmech.2013.08.009)

AUTORES / AUTHORS: - Imramovsky A; Jorda R; Pauk K; Reznickova E; Dusek J; Hanusek J; Krystof V

INSTITUCIÓN / INSTITUTION: - Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentska 573, 53210 Pardubice, Czech Republic. Electronic address: Ales.Imramovsky@upce.cz.

RESUMEN / SUMMARY: - Various substituted 2-hydroxy-N-(arylalkyl)benzamides were prepared and screened for antiproliferative and cytotoxic activity in cancer cell lines in vitro. Five compounds, out of 33 showed single-digit micromolar IC50 values against several human cancer cell lines. One of the most potent compounds N-([®]-1-(4-chlorophenylcarbamoyl)-2-phenylethyl)-5-chloro-2-hydroxybenzamide (6k) reduced proliferation and induced apoptosis in the melanoma cell line G361 in a dose-dependent manner, as shown by decrease in 5-bromo-2'-deoxyuridine incorporation and increase in several apoptotic markers, including subdiploid population increase, activation of caspases and site-specific poly-(ADP-ribose)polymerase (PARP) cleavage.

[748]

TÍTULO / TITLE: - Parthenolide and costunolide reduce microtentacles and tumor cell attachment by selectively targeting detyrosinated tubulin independent from NF-kappaB inhibition.

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

REVISTA / JOURNAL: - Breast Cancer Res. 2013 Sep 13;15(5):R83.

●● Enlace al texto completo (gratis o de pago) [1186/bcr3477](https://doi.org/10.1186/bcr3477)

AUTORES / AUTHORS: - Whipple RA; Vitolo MI; Boggs AE; Charpentier MS; Thompson K; Martin SS

INSTITUCIÓN / INSTITUTION: - Marlene and Stewart Greenebaum NCI Cancer Center, University of Maryland School of Medicine, Bressler Bldg, Rm 10-29, 22 S, Greene Street, Baltimore, MD 21201, USA. ssmartin@som.umaryland.edu.

RESUMEN / SUMMARY: - INTRODUCTION: Detyrosinated tubulin, a post-translational modification of alpha-tubulin and a hallmark of stable microtubules, has gained recent attention given its association with tumor progression, invasiveness, and chemoresistance. We also recently reported that epithelial-to-mesenchymal transition (EMT) promotes tubulin detyrosination through tubulin tyrosine ligase (TTL) suppression. Furthermore, detyrosinated tubulin-enriched membrane protrusions, termed microtentacles (McTN), facilitate tumor cell reattachment to endothelial layers. Given the induction of EMT associated with inflammation and cancer progression, we tested anti-inflammatory nuclear factor-kappaB (NF-kappaB) inhibitors on a panel of human breast carcinoma cells to examine their effects on detyrosinated tubulin to identify more specific tubulin-directed anti-cancer treatments. METHODS: Using metastatic human breast carcinoma cells MDA-MB-157, MDA-MB-436, and Bt-549, we measured the impact of NF-kappaB inhibitors parthenolide, costunolide, and resveratrol on detyrosinated tubulin using protein expression analysis and immunofluorescence. A luciferase reporter assay and a viability screen were performed to determine if the effects were associated with their NF-kappaB inhibitory properties or were a result of apoptosis. Real-time monitoring of cell-substratum attachment was measured utilizing electrical impedance across microelectronic sensor arrays. We compared the selectivity of the NF-kappaB inhibitors to specifically target detyrosinated tubulin with traditional tubulin-targeted therapeutics, paclitaxel and colchicine, throughout the study. RESULTS: Sesquiterpene lactones, parthenolide and costunolide, selectively decrease detyrosinated tubulin independent of their inhibition of NF-kappaB. Live-cell scoring of suspended cells treated with parthenolide and costunolide show reduction in the frequency of microtentacles and inhibition of reattachment. Structural analysis shows that parthenolide and costunolide can decrease detyrosinated microtubules without significantly disrupting the overall microtubule network or cell viability. Paclitaxel and colchicine display indiscriminate disruption of the microtubule network. CONCLUSIONS: Our data demonstrate that selective targeting of detyrosinated tubulin with parthenolide and costunolide can reduce McTN frequency and inhibit tumor cell reattachment. These actions are independent of their effects on NF-kappaB inhibition presenting a novel anti-cancer property and therapeutic opportunity to selectively target a stable subset of microtubules in circulating tumor cells to reduce metastatic potential with less toxicity in breast cancer patients.

[749]

TÍTULO / TITLE: - 3rd generation ABL kinase inhibitor and Philadelphia chromosome positive leukemia.

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

REVISTA / JOURNAL: - Rinsho Ketsueki. 2013 Oct;54(10):1682-6.

AUTORES / AUTHORS: - Tauchi T

[750]

TÍTULO / TITLE: - Classifier-free, integrated genomic predictions of prostate cancer recurrence.

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

REVISTA / JOURNAL: - Stud Health Technol Inform. 2013;192:1177.

AUTORES / AUTHORS: - Shivade C; Chen JL

INSTITUCIÓN / INSTITUTION: - Department of Computer Science Engineering, The Ohio State University, Columbus, OH.

RESUMEN / SUMMARY: - Genomic predictions of clinical outcome are a core promise of the Human Genome Project. Yet actionable biomarkers in clinical medicine are confounded by patient heterogeneity as patient phenotypes are rarely well characterized and often poorly understood. Furthermore, standard predictive algorithms rely on a priori knowledge of discrete phenotypes for feature selection and training. To address this limitation, we develop a classifier-free algorithm that matches individual patients to other patient outcomes based on optimized clinicopathologic feature integration and molecular pathway similarity using the K-nearest neighbor. By identifying the best matches within the collection of patient data, we are able to return the desired prediction. In prostate cancer, we demonstrate the algorithm's ability to predict cancer recurrence without the need for supervised learning techniques in independent datasets with a recall and precision of 78%. Importantly, the predictor is microarray platform independent, scalable and simple to implement. Taken together, this method provides an exciting foundation from data-driven, clinical decision-making may arise.

[751]

TÍTULO / TITLE: - Central nervous system prophylaxis with intrathecal liposomal cytarabine in diffuse large B-cell lymphomas.

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

REVISTA / JOURNAL: - Pol Arch Med Wewn. 2013 Aug 8. pii: AOP_13_043.

AUTORES / AUTHORS: - Krawczyk K; Jurczak W; Dlugosz-Danecka M; Zauska-Giza A; Dietczenia J; Wrobel T; Skotnicki AB

RESUMEN / SUMMARY: - INTRODUCTION Central nervous system (CNS) dissemination is a serious and potentially fatal complication in lymphoma patients, associated with a particularly poor prognosis (median progression free survival [PFS] of 4-6 months). Although CNS prophylaxis of high risk cases is considered necessary, there are no clear guidelines for selecting patients or treatment regimen. OBJECTIVES Investigate and assess the safety and efficacy of CNS prophylaxis with intrathecal (IT) liposomal

cytarabine. PATIENTS AND METHODS Seventy nine patients with diffuse large B-cell lymphoma (DLBCL) - 83.5% and primary mediastinal large B-cell lymphoma (PMBCL) - 16.5% and considered to be at high risk of developing CNS involvement, who were diagnosed and treated in the Department of Hematology in Krakow and Wroclaw between 2009-2012. Median age was 48.5 years (20-79), in the subgroup with DLBCL diagnosis 50.1 (20-79) and with PMBCL 40.5 (28-57). There were 46 males and 33 females. RESULTS Adverse reactions after IT liposomal cytarabine reported in 59 patients (74.68%), were regarded as severe in 7 cases. The most common side effect was headache (67.1%). During anti-lymphoma therapy and prophylaxis, functional status assessed by Karnofsky score improved in 56 (70.88%) patients and remained unchanged in the rest of the cases. At median follow-up time of 28 months (range 1.4-52.1), neither median overall survival (OS) nor PFS were reached (projected PFS and OS at 48 months is 86.1 % and 90.1% respectively). CONCLUSIONS Both effectiveness and toxicity profile of CNS prophylaxis with liposomal cytarabine encourages the use of this treatment in high risk lymphoma patients.

[752]

TÍTULO / TITLE: - 131I-rituximab treatment in patient with relapsed non-Hodgkin's lymphoma: the first case report in Thailand.

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

REVISTA / JOURNAL: - J Med Assoc Thai. 2013 Jun;96(6):756-60.

AUTORES / AUTHORS: - Kositwattanarerk A; Changmuang W; Sangsuriyan J; Thongklam K; Sritara C; Utamakul C; Chamroonrat W; Thamnirat K; Anongpornyochkul Y; Chancharunee S

INSTITUCIÓN / INSTITUTION: - Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.
arpakorn13521@gmail.com

RESUMEN / SUMMARY: - Radioimmunotherapy (RIT) with 131-rituximab is a safe and effective treatment in patients with relapsed, refractory follicular lymphoma. The authors demonstrated the first case of 131-rituximab treatment in the patient with relapsed non-Hodgkin's lymphoma (NHL) in Thailand. There was no immediate complication after treatment. Impressive treatment response occurred.

[753]

TÍTULO / TITLE: - The flip side of doxorubicin: Inflammatory and tumor promoting cytokines.

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

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 12;14(9).

AUTORES / AUTHORS: - Dent P

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery; Massey Cancer Center; Virginia Commonwealth University; Richmond VA USA.

[754]

TÍTULO / TITLE: - Mycophenolic Acid for lymphomatoid papulosis.

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

REVISTA / JOURNAL: - J Cutan Med Surg. 2013 Oct 1;17(5):332-4.

AUTORES / AUTHORS: - Champagne T; Walsh S

RESUMEN / SUMMARY: - Background:Lymphomatoid papulosis is a rare CD30+ lymphoproliferative T-cell disorder with limited effective treatments.Objective:We describe the case of a 50-year-old woman diagnosed with lymphomatoid papulosis who was unable to access phototherapy and who failed to clear while on systemic treatment with methotrexate.Methods:The patient was initiated on mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, at a dose of 2 g divided twice daily.Results:MMF produced a rapid response with complete clearing within 8 weeks, and the patient has been successfully maintained for 2 years at the same dose with no noted side effects. Other patients in our clinic have had similar success.Conclusions:Mycophenolic acid is a safe and well-tolerated therapy for lymphomatoid papulosis.

[755]

TÍTULO / TITLE: - Preparation of betulinic acid derivatives by chemical and biotransformation methods and determination of cytotoxicity against selected cancer cell lines.

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

REVISTA / JOURNAL: - Eur J Med Chem. 2013 Aug 7;68C:121-131. doi: 10.1016/j.ejmech.2013.07.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejmech.2013.07.012](https://doi.org/10.1016/j.ejmech.2013.07.012)

AUTORES / AUTHORS: - Baratto LC; Porsani MV; Pimentel IC; Pereira Netto AB; Paschke R; Oliveira BH

INSTITUCIÓN / INSTITUTION: - Departamento de Química, Universidade Federal do Paraná, Centro Politécnico, 81531-970, CP 19081 Curitiba, PR, Brazil.

RESUMEN / SUMMARY: - Several novel 2,4-dinitrophenylhydrazone betulinic acid derivatives have been prepared by chemical and biotransformation methods using fungi and carrot cells. Some compounds showed significant cytotoxicity and selectivity against some tumor cell lines. The most active, 3-[(2,4-dinitrophenyl)hydrazono]lup-(20R)-29-oxolupan-28-oic acid, showed IC50 values between 1.76 and 2.51 µM against five human cancer cell lines. The most selective, 3-hydroxy-20-[(2,4-dinitrophenyl)hydrazono]-29-norlupan-28-oic acid, was five to seven times more

selective for cancer cells when compared to fibroblasts. Cell cycle analysis and apoptosis induction were studied for the most active derivatives.

[756]

TÍTULO / TITLE: - Alteration of cancer stem cell-like phenotype by histone deacetylase inhibitors in squamous cell carcinoma of the head and neck.

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

REVISTA / JOURNAL: - Cancer Sci. 2013 Aug 30. doi: 10.1111/cas.12271.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12271](#)

AUTORES / AUTHORS: - Chikamatsu K; Ishii H; Murata T; Sakakura K; Shino M; Toyoda M; Takahashi K; Masuyama K

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology-Head and Neck Surgery, Gunma University Graduate School of Medicine.

RESUMEN / SUMMARY: - Recent progression in the understanding of stem cell biology has greatly facilitated the identification and characterization of cancer stem cells (CSCs). Moreover, evidence has accumulated indicating that conventional cancer treatments are potentially ineffective against CSCs. Histone deacetylase inhibitors (HDACi) have multiple biologic effects consequent to alterations in the patterns of acetylation of histones and are a promising new group of anticancer agents. In this study, we investigated the effects of two HDACi, suberoylanilide hydroxamic acid (SAHA) and trichostatin A (TSA), on two CD44+ cancer stem-like cell lines from SCCHN cultured in serum-free medium containing epidermal growth factor and basic fibroblast growth factor. HDACi inhibited the growth of SCCHN cell lines in a dose-dependent manner as measured by MTS assays. Moreover, HDACi induced cell cycle arrest and apoptosis in these SCCHN cell lines. Interestingly, the expression of cancer stem cell markers, CD44 and ABCG2, on SCCHN cell lines was decreased by HDACi treatment. In addition, HDACi decreased mRNA expression levels of stemness-related genes and suppressed the epithelial-mesenchymal transition phenotype of CSCs. As expected, the combination of HDACi and chemotherapeutic agents, including cisplatin and docetaxel, had a synergistic effect on SCCHN cell lines. Taken together, our data indicate that HDACi not only inhibit the growth of SCCHN cell lines by inducing apoptosis and cell cycle arrest, but also alter the cancer stem cell phenotype in SCCHN, raising the possibility that HDACi may have therapeutic potential for cancer stem cells of SCCHN. This article is protected by copyright. All rights reserved.

[757]

TÍTULO / TITLE: - Gelsolin and Ceruloplasmin as Potential Predictive Biomarkers for Cervical Cancer by 2D-DIGE Proteomics Analysis.

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

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) 1007/s12253-013-9670-9

AUTORES / AUTHORS: - Lokamani I; Looi ML; Md Ali SA; Mohd Dali AZ; Ahmad Annuar MA; Jamal R

INSTITUCIÓN / INSTITUTION: - UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia, Level 7, Clinical Block, UKM Medical Centre, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur, Malaysia.

RESUMEN / SUMMARY: - This study aimed to identify candidate proteins which may serve as potential biological markers for cervical cancer using 2D-DIGE. Serum samples of controls, patients with cervical intraepithelial neoplasia grade 3 (CIN 3), squamous cell carcinoma of early (SCC I and II) and late (SCC III and IV) stage were subjected to 2D-DIGE. Differentially expressed spots were identified by tandem mass spectrometry. Validation of candidate proteins in serum and tissue samples were then performed by ELISA and immunohistochemistry (IHC) analysis respectively. A total of 20 differentially expressed proteins were identified. These proteins were found to play key roles in the apoptosis pathway, complement system, various types of transportation such as hormones, fatty acids, lipid, vitamin E and drug transportation, coagulation cascade, regulation of iron and immunologic response. Based on their functional relevancy to the progression of various cancers, 4 proteins namely the complement factor H, CD5-like antigen, gelsolin and ceruloplasmin were chosen for further validation using ELISA. Biological network analysis showed that ceruloplasmin and gelsolin are closely interacted with the oncogene NF-kappaB. These two proteins were further validated using the IHC. Gelsolin and ceruloplasmin may serve as potential predictive biomarkers for the progression of high grade lesions.

[758]

TÍTULO / TITLE: - A balance of interleukin-12 and -23 in cancer.

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

REVISTA / JOURNAL: - Trends Immunol. 2013 Aug 13. pii: S1471-4906(13)00111-7. doi: 10.1016/j.it.2013.07.004.

●● Enlace al texto completo (gratis o de pago) 1016/j.it.2013.07.004

AUTORES / AUTHORS: - Ngiow SF; Teng MW; Smyth MJ

INSTITUCIÓN / INSTITUTION: - Immunology in Cancer and Infection Laboratory, Queensland Institute of Medical Research, Herston, 4006, Queensland, Australia.

RESUMEN / SUMMARY: - Interleukin (IL)-12 and IL-23 share the IL-12p40 molecule. IL-12 promotes T helper (Th)1 immunity and IL-23 promotes Th17 immunity, and it has recently become apparent that the balance between IL-12 and IL-23 is important in carcinogenesis. A series of studies demonstrated that, where tumor initiation, growth, and metastasis are concerned, IL-12 may act independently of interferon (IFN)-gamma, and IL-23 independently of IL-17^a. This review explores the activity of IL-23 in

carcinogenesis. In the context of the tumor-inhibitory effects of IL-12, and tumor-promoting effects of IL-23, we discuss the use of anti-IL-12p/23 monoclonal antibodies (mAbs) in autoimmune inflammatory disorders and the alternative specific neutralization of IL-23.

[759]

TÍTULO / TITLE: - SK-216, an inhibitor of plasminogen activator inhibitor-1, limits tumor progression and angiogenesis.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Aug 29.

- Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0041](#)

AUTORES / AUTHORS: - Masuda T; Hattori N; Senoo T; Akita S; Ishikawa N; Fujitaka K; Haruta Y; Murai H; Kohno N

INSTITUCIÓN / INSTITUTION: - 1Molecular and Internal medicine, Graduate School of Biomedical & Health Sciences, Hiroshima University.

RESUMEN / SUMMARY: - Plasminogen activator inhibitor-1 (PAI-1), which can be produced by host and tumor cells in the tumor microenvironment, is intimately involved in tumor progression. In the present study, to pursue the possibility that PAI-1 could be a therapeutic target in the management of malignancy, SK-216, a specific PAI-1 inhibitor, was orally administered to wild-type mice that were subcutaneously implanted or intravenously injected with either PAI-1-secreting Lewis lung carcinoma (LLC) or PAI-1-non-secreting B16 melanoma cells. The systemic administration of SK-216 was found to reduce the size of subcutaneous tumors and the extent of metastases, regardless of PAI-1-secretion levels from the tumor cells. SK-216 also reduced the extent of angiogenesis in the tumors and inhibited VEGF-induced migration and tube formation by human umbilical vein endothelial cells in vitro. Then, to determine whether host or tumor PAI-1 was more crucial in tumor progression and angiogenesis, PAI-1-deficient or wild-type mice were subcutaneously implanted or intravenously injected with LLC or PAI-1 knockdown LLC cells. Tumor progression was shown to be controlled by the presence of host PAI-1 and not affected by the PAI-1 levels in the tumors. Similarly, host PAI-1 played a more crucial role in tumor angiogenesis than did tumor PAI-1. These observations suggest that regardless of the PAI-1 levels in the tumor, the systemic administration of SK-216 exerts an antitumor effect through its interaction with host PAI-1. This antitumor effect might be mediated by the anti-angiogenic properties of SK-216.

[760]

TÍTULO / TITLE: - Targeting plasminogen activator inhibitor-1 inhibits angiogenesis and tumor growth in a human cancer xenograft model.

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

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0500](#)

AUTORES / AUTHORS: - Gomes-Giacoia E; Miyake M; Goodison S; Rosser CJ

INSTITUCIÓN / INSTITUTION: - 1Cancer Research Institute, MD Anderson Cancer Center Orlando.

RESUMEN / SUMMARY: - Cancers of the urinary bladder result in aggressive and highly angiogenic tumors for which standard treatments have only limited success. Patients with advanced disease have a 5-year survival rate of <20%, and no new anti-cancer agent has been successfully introduced into the clinic armamentarium for the treatment of bladder cancer in over 20 years. Investigations have identified plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor, as being highly expressed in several malignancies, including bladder cancer, in which high expression is associated with a poor prognosis. In this study, we evaluated PAI-1 as a potential therapeutic target for bladder cancer. PAI-1 expression was manipulated in a panel of cell lines and functional inhibition was achieved using the small molecule tiplaxtinin. Reduction or inhibition of PAI-1 resulted in the reduction of cellular proliferation, cell adhesion, and colony formation, and the induction of apoptosis and anoikis in vitro. Treatment of T24 xenografts with tiplaxtinin resulted in inhibition of angiogenesis and induction of apoptosis, leading to a significant reduction in tumor growth. Similar results were obtained through evaluation of the human cervical cancer HeLa cell line, showing that PAI-1 mediated effects are not restricted to tumor cells of bladder origin. Collectively, these data show that targeting PAI-1 may be beneficial and support the notion that novel drugs such as tiplaxtinin could be investigated as anti-cancer agents.

[761]

TÍTULO / TITLE: - Tumor growth retardation and chemosensitizing action of fatty acid synthase inhibitor orlistat on T cell lymphoma: Implication of reconstituted tumor microenvironment and multidrug resistance phenotype.

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

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Sep 20. pii: S0304-4165(13)00401-7. doi: 10.1016/j.bbagen.2013.09.020.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbagen.2013.09.020](#)

AUTORES / AUTHORS: - Kumar A; Singh SM

INSTITUCIÓN / INSTITUTION: - School of Biotechnology, Banaras Hindu University, Varanasi 221005, India.

RESUMEN / SUMMARY: - BACKGROUND: Orlistat, a fatty acid synthase (FASN) inhibitor, has been demonstrated to inhibit tumor cell survival. However, the mechanism(s) of its tumor growth retarding action against malignancies of hematological origin remains unclear. It is also not understood if the antitumor action of orlistat implicates modulated susceptibility of tumor cell to anticancer drugs. Therefore, the present investigation focuses to study the antitumor and chemosensitizing action of orlistat in a murine host bearing a progressively growing T cell lymphoma. METHODS: Tumor-bearing mice were administered with vehicle alone or containing orlistat followed by administration of PBS with or without cisplatin. Tumor progression and survival of tumor-bearing host were monitored along with analysis of tumor cell survival and apoptosis. Tumor ascitic fluid was examined for pH, NO and cytokines. Expression of genes and proteins was investigated by RT-PCR and western blot respectively. ROS was analyzed by DCFDA staining and FASN activity by spectrophotometry. RESULTS: Orlistat administration to tumor-bearing mice resulted in tumor growth retardation, prolonged life span, declined tumor cell survival and chemosensitization to cisplatin. It was accompanied by increased osmotic fragility, modulated acidosis, expression of ROS, NO, cytokines, MCT-1 and VH+ ATPase, Bcl2, Caspase-3, P53, inhibited FASN activity and declined expression of MDR and MRP-1 proteins. CONCLUSION AND SIGNIFICANCE: Orlistat manifests antitumor and chemosensitizing action implicating modulated regulation of cell survival, reconstituted-tumor microenvironment and altered MDR phenotype. These observations indicate that orlistat could be utilized as an adjunct regimen for improving antitumor efficacy of cisplatin.

[762]

TÍTULO / TITLE: - Why Proteasome Inhibitors Cannot ERADicate Multiple Myeloma.

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

REVISTA / JOURNAL: - Cancer Cell. 2013 Sep 9;24(3):275-7. doi: 10.1016/j.ccr.2013.08.014.

●● Enlace al texto completo (gratis o de pago) [1016/j.ccr.2013.08.014](#)

AUTORES / AUTHORS: - Orłowski RZ

INSTITUCIÓN / INSTITUTION: - Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA. Electronic address: rorlow@mdanderson.org.

RESUMEN / SUMMARY: - Proteasome inhibitors are key parts of our armamentarium against multiple myeloma, but the disease can become resistant through poorly defined mechanisms. In this issue of Cancer Cell, Leung-Hagesteijn and colleagues describe XBP1s(-) subpopulations of tumor cells that are resistant to bortezomib and may account for therapeutic failures in the clinic.

[763]

TÍTULO / TITLE: - ERCC1 C8092A (rs3212986) polymorphism as a predictive marker in esophageal cancer patients treated with cisplatin/5-FU-based neoadjuvant therapy.

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

REVISTA / JOURNAL: - Pharmacogenet Genomics. 2013 Aug 18.

●● Enlace al texto completo (gratis o de pago) [1097/FPC.0b013e3283653afc](#)

AUTORES / AUTHORS: - Rumiato E; Cavallin F; Boldrin E; Cagol M; Alfieri R; Basso D; Castoro C; Ancona E; Amadori A; Ruol A; Saggiaro D

INSTITUCIÓN / INSTITUTION: - aImmunology and Molecular Oncology Unit bOncological Surgery Unit, Veneto Institute of Oncology IOV-IRCCS Departments of cLaboratory Medicine dSurgical Sciences, Oncology and Gastroenterology, University of Padova, Padova, Italy.

RESUMEN / SUMMARY: - OBJECTIVE: At present, no consensus exists on the beneficial effect of preoperative cisplatin/5-fluorouracil (5-FU)-based chemotherapy versus primary surgery in the management of patients with esophageal cancer. The aim of this study was to evaluate the impact of some relevant genetic polymorphisms, within drug-related and DNA repair genes, on the clinical outcome of esophageal cancer patients subjected to cisplatin/5-FU-based neoadjuvant treatment. METHODS: DNA from 143 esophageal cancer patients, 63 receiving neoadjuvant therapy and 80 receiving primary surgery, was analyzed for the following polymorphisms: the GSTM1 null, GSTT1 null, and GSTP1 Ile105Val (rs16953) in glutathione S-transferase (GST) family, 2 in thymidylate synthase (TS) gene, and the ERCC1 Asn118Asn (rs11615), ERCC1 C8092A (rs3212986), XPD/ERCC2 Asp312Asn (rs1799793), and XPD/ERCC2 Lys751Gln (rs13181) of the nucleotide excision repair pathway. RESULTS: We found that the ERCC1 rs3212986, although not associated with therapeutic response, is an independent predictive marker of better outcome in a cisplatin/5-FU-based neoadjuvant setting (hazard ratio: 0.38, 95% confidence interval: 0.2-0.73, P=0.008). In contrast, no association with clinical outcome was observed for this polymorphism in the primary surgery group. CONCLUSION: Our study indicates the ERCC1 rs3212986 as a predictive marker in the cisplatin/5-FU-based neoadjuvant setting, and also suggests its use as a marker to select the appropriate therapeutic approach in esophageal cancer patients.

[764]

TÍTULO / TITLE: - Multiple myeloma: chromosomal abnormalities, clinical features and prognosis.

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

REVISTA / JOURNAL: - Rinsho Ketsueki. 2013 Oct;54(10):1856-66.

AUTORES / AUTHORS: - Ishida T

[765]

TÍTULO / TITLE: - CXC Chemokine Receptor 4 Expression, CXC Chemokine Receptor 4 Activation, and Wild-Type Nucleophosmin Are Independently Associated With Unfavorable Prognosis in Patients With Acute Myeloid Leukemia.

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

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Sep 11. pii: S2152-2650(13)00230-9. doi: 10.1016/j.clml.2013.05.013.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.05.013

AUTORES / AUTHORS: - Konoplev S; Lin P; Yin CC; Lin E; Nogueras Gonzalez GM; Kantarjian HM; Andreeff M; Medeiros LJ; Konopleva M

INSTITUCIÓN / INSTITUTION: - Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX. Electronic address: skonople@mdanderson.org.

RESUMEN / SUMMARY: - BACKGROUND: CXC chemokine receptor 4 (CXCR4) is activated by phosphorylation and essential for migration of hematopoietic precursors to bone marrow. CXCR4 overexpression predicts unfavorable prognosis in patients with acute myeloid leukemia (AML). Nucleophosmin (NPM1) mutation is the most frequent genetic abnormality in patients with AML and predicts a favorable prognosis. In vitro studies have suggested that mutant nucleophosmin (NPM) decreases CXCR4-mediated chemotaxis by downregulating CXCR4, thereby linking the NPM and CXCR4 pathways. PATIENTS AND METHODS: In a group of 117 untreated adults with AML, we used immunohistochemistry to assess bone marrow specimens for CXCR4 and phosphorylated CXCR4 (pCXCR4) expression. All cases also were analyzed for NPM1 mutations using polymerase chain reaction-based methods. RESULTS: CXCR4 expression was detected in 75 patients (64%), and pCXCR4 expression was detected in 31 patients (26%). NPM1 mutations were detected in 63 patients (54%). NPM1 mutations did not correlate with CXCR4 ($P = .212$) or pCXCR4 ($P = .355$) expression. The median 5-year overall survival was 27% (95% confidence interval, 19-36), with a median follow-up of 8 months (95% confidence interval, 6-15). In a multivariate Cox proportional hazards model, reduced overall and progression-free survival rates were associated with a history of antecedent hematologic disorder, failure to achieve complete remission, thrombocytopenia, unfavorable cytogenetics, CXCR4 expression, and wild-type NPM1. pCXCR4 expression was independently associated with shorter progression-free survival. CONCLUSIONS: There is no correlation between NPM1 mutations and CXCR4 or pCXCR4 expression, suggesting that the CXCR4 and NPM pathways act independently in adult AML.

[766]

TÍTULO / TITLE: - ERCC1 is a prognostic biomarker in locally advanced head and neck cancer: results from a randomised, phase II trial.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Sep 24. doi: 10.1038/bjc.2013.576.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.576](#)

AUTORES / AUTHORS: - Bauman JE; Austin MC; Schmidt R; Kurland BF; Vaezi A; Hayes DN; Mendez E; Parvathaneni U; Chai X; Sampath S; Martins RG

INSTITUCIÓN / INSTITUTION: - Departments of Medicine, Biostatistics and Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA.

RESUMEN / SUMMARY: - Background: Cisplatin-radiotherapy is a preferred standard for locally advanced, head and neck squamous cell carcinoma (HNSCC). However, the cisplatin-attributable survival benefit is small and toxicity substantial. A biomarker of cisplatin resistance could guide treatment selection and spare morbidity. The ERCC1-XPF nuclease is critical to DNA repair pathways resolving cisplatin-induced lesions. Methods: In a phase II trial, patients with untreated Stage III-IVb HNSCC were randomised to cisplatin-radiotherapy with/without erlotinib. Archived primary tumours were available from 90 of 204 patients for this planned substudy. Semi-quantitative ERCC1 protein expression (H-score) was determined using the FL297, 4F9, and 8F1 antibodies. The primary analysis evaluated the relationship between continuous ERCC1 protein expression and progression-free survival (PFS). Secondary analyses included two pre-specified ERCC1 cutpoints and performance in HPV-associated disease. Results: Higher ERCC1 expression was associated with inferior PFS, as measured by the specific antibodies FL297 (HR=2.5, 95% CI=1.1-5.9, P=0.03) and 4F9 (HR=3.0, 95% CI=1.2-7.8, P=0.02). Patients with increased vs decreased/normal ERCC1 expression experienced inferior PFS (HR=4.8 for FL297, P=0.003; HR=5.5 for 4F9, P=0.007). This threshold remained prognostic in HPV-associated disease. Conclusion: ERCC1-XPF protein expression by the specific FL297 and 4F9 antibodies is prognostic in patients undergoing definitive cisplatin-radiotherapy for HNSCC, irrespective of HPV status. British Journal of Cancer advance online publication, 24 September 2013; doi:10.1038/bjc.2013.576 www.bjcancer.com. \$!"1060.95\$!"TATATAT - Br J Cancer

[767]

TÍTULO / TITLE: - Prognostic Significance of Human Epidermal Receptor (HER)- 3 Immunohistochemical Expression in Patients with Metastatic Breast Cancer.

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

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(7):4115-9.

AUTORES / AUTHORS: - Olmez OF; Evrensel T; Cubukcu E; Ugras N; Avci N; Canhoroz M; Deligonul A; Hartavi M; Olmez F; Cubukcu S; Tolunay S; Kurt E; Kanat O; Manavoglu O

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Uludag University Medical School, Bursa, Turkey E-mail : ofolmez@uludag.edu.tr.

RESUMEN / SUMMARY: - Background: Previous reports have shown that human epidermal receptor (HER)-3 overexpression may be associated with poor prognosis in

patients with breast cancer, but results have been conflicting. In this study, we sought to investigate the prognostic significance of HER-3 immunohistochemical expression in patients with metastatic breast cancer. Methods: We retrospectively analyzed HER-3 immunohistochemical expression profiles in 45 paraffin-embedded specimens from patients who had been treated between 1996 and 2006 in the Department of Oncology of the Uludag University School of Medicine, Bursa, Turkey. Membranous or cytoplasmic dominant expression patterns of HER-3 were analyzed using the Rajkumar score and a cytoplasmic 4-point scoring system, respectively. Progression-free survival (PFS) and overall survival (OS) served as the main outcome measures. Results: The median PFS in the study participants was 9 months (interquartile range: 4.5-13 months), whereas the median OS was 20 months (interquartile range: 7.5-28 months). Categorization of the patient population according to HER-3 positive immunohistochemical expression did not reveal any statistically significant difference in terms of both PFS ($p=0.70$) and OS ($p=0.81$). The results of multivariable Cox regression analysis indicated that tumor size was the only independent predictor of PFS, whereas estrogen and progesterone receptor status was independently associated with OS. Conclusions: HER-3 immunohistochemical expression did not correlate with outcomes in Turkish patients with metastatic breast cancer. Although our results suggest that HER-3 expression in cancer specimens is not of prognostic significance, further prospective studies are warranted to confirm these results.

[768]

TÍTULO / TITLE: - Study of Imatinib Treatment Patterns and Outcomes Among US Veteran Patients With Philadelphia Chromosome-Positive Chronic Myeloid Leukemia.

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

REVISTA / JOURNAL: - J Oncol Pract. 2013 Sep 1;9(5):e212-9. doi: 10.1200/JOP.2012.000822. Epub 2013 May 28.

●● Enlace al texto completo (gratis o de pago) [1200/JOP.2012.000822](#)

AUTORES / AUTHORS: - Vander Velde N; Chen L; Guo A; Sharma H; Marynchenko M; Wu EQ; Liu J; Yang H; Shi L

INSTITUCIÓN / INSTITUTION: - Tulane University; Southeast Louisiana Veterans Health Care System, New Orleans, LA; Novartis Pharmaceuticals Corporation, East Hanover, NJ; and Analysis Group, Boston, MA.

RESUMEN / SUMMARY: - PURPOSE: This study investigated the treatment patterns and outcomes for US veteran patients with chronic myeloid leukemia-chronic phase (CML-CP) initiated on imatinib (IM). PATIENTS AND METHODS: Patients (age ≥ 18 years) with at least one CML diagnosis (International Classification of Diseases, Ninth Edition Clinical Modification: 205.1x) during the period January 1, 2000, to June 30, 2011, and initiated on IM as first-line therapy were identified in the VISN 16 data warehouse (N = 137). Accelerated and blastic phases (AP/BP) were identified on the basis of WHO

classification using complete blood count (CBC) data. Rates of IM dose adjustment, discontinuation, and switching to another drug therapy were estimated. Time to discontinuation, progression to AP/BP, and survival were assessed using Kaplan-Meier analysis (KM). RESULTS: During follow-up, 19.0% of patients had at least one dose increase; of these, 19.2% switched to another therapy. Dose reductions occurred in 25.6% of patients. Among patients who discontinued IM (n = 74; 54.0%), whereas 16.2% switched to other therapies, 27.0% neither restarted IM nor switched to other therapies. KM showed that 25.6% and 42.4% of patients discontinued IM treatment by year 1 and 2, and 8.1% and 16.0% demonstrated disease progression by year 1 and 2, respectively. Among patients who experienced disease progression (n = 28), 32.1% continued IM postprogression, 32.1% discontinued IM before progression, 28.6% discontinued IM postprogression without switching, and 7.1% switched to other therapies postprogression. The mortality rates were 3.0% and 9.5% after IM initiation, and 21.7% and 42.7% after disease progression by year 1 and 2, respectively. CONCLUSION: In this veteran population, a substantial number of IM-treated patients, including those with disease progression, either discontinued or interrupted IM use without switching to other therapies.

[769]

TÍTULO / TITLE: - Assessment of the Prognostic Value of Two Common Variants of BRCA1 and BRCA2 Genes in Ovarian Cancer Patients Treated with Cisplatin and Paclitaxel: A Gynecologic Oncology Group Study.

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

REVISTA / JOURNAL: - Front Oncol. 2013;3:206. doi: 10.3389/fonc.2013.00206.

●● Enlace al texto completo (gratis o de pago) [3389/fonc.2013.00206](#)

AUTORES / AUTHORS: - Tian CQ; Darcy KM; Krivak TC; Deloia JA; Armstrong D; Davis W; Zhao H; Moysich K; Ambrosone CB

INSTITUCIÓN / INSTITUTION: - Gynecologic Oncology Group Statistical and Data Center , Buffalom, NY , USA.

RESUMEN / SUMMARY: - Purpose: BRCA1/BRCA2 germline mutations appear to enhance the platinum-sensitivity, but little is known about the prognostic relevance of polymorphisms in BRCA1/BRCA2 in epithelial ovarian cancer (EOC). This study evaluated whether common variants of BRCA1/BRCA2 are associated with progression-free survival (PFS) and overall survival (OS) in patients with advanced stage sporadic EOC. Experimental Design: The allelic frequency of BRCA1 (2612C > T, P871L-rs799917) and BRCA2 (114^a > C, N372H-rs144848) were determined in normal blood DNA from women in Gynecologic Oncology Group protocol #172 phase III trial with optimally resected stage III EOC treated with intraperitoneal or intravenous cisplatin and paclitaxel (C + P). Associations between polymorphisms and PFS or OS were assessed. Results: Two hundred and thirty-two women were included for analyses. African Americans (AA) had different distributions for the two

polymorphisms from Caucasians and others. For non-AA patients, the genotype for BRCA1 P871L was distributed as 38% for CC, 49% for CT, and 13% for TT. Median PFS was estimated to be 31, 21, and 21 months, respectively. After adjusting for cell type, residual disease, and chemotherapy regimen, CT/TT genotypes were associated with a 1.40-fold increased risk of disease progression [95% confidence interval (CI) = 1.00-1.95, $p = 0.049$]. After removing seven patients with known BRCA1 germline mutations, the hazard ratio (HR) was 1.36 (95% CI = 0.97-1.91, $p = 0.073$). The association between BRCA1 P871L and OS was not significant (HR = 1.25, 95% CI = 0.88-1.76, $p = 0.212$). Genotype distribution of BRCA2 N372H among non-AA patients was 50, 44, and 6% for AA, AC, and CC, respectively and there is no evidence that this BRCA2 polymorphism was related to PFS or OS. Conclusion: Polymorphisms in BRCA1 P871L or in BRCA2 N372H were not associated with either PFS or OS in women with optimally resected, stage III EOC treated with cisplatin and paclitaxel.

[770]

TÍTULO / TITLE: - Cancer Stem Cell Gene Profile as Predictor of Relapse in High Risk Stage II and Stage III, Radically Resected Colon Cancer Patients.

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

REVISTA / JOURNAL: - PLoS One. 2013 Sep 4;8(9):e72843. doi: 10.1371/journal.pone.0072843.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072843](https://doi.org/10.1371/journal.pone.0072843)

AUTORES / AUTHORS: - Giampieri R; Scartozzi M; Loretelli C; Piva F; Mandolesi A; Lezoche G; Prete MD; Bittoni A; Faloppi L; Bianconi M; Cecchini L; Guerrieri M; Bearzi I; Cascinu S

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, AO Ospedali Riuniti-UNIVPM, Ancona, Italy.

RESUMEN / SUMMARY: - Clinical data indicate that prognostic stratification of radically resected colorectal cancer based on disease stage only may not be always be adequate. Preclinical findings suggest that cancer stem cells may influence the biological behaviour of colorectal cancer independently from stage: objective of the study was to assess whether a panel of stemness markers were correlated with clinical outcome in resected stage II and III colon cancer patients. A panel of 66 markers of stemness were analysed and thus patients were divided into two groups (A and B) with most patients clustering in a manner consistent with different time to relapse by using a statistical algorithm. A total of 62 patients were analysed. Thirty-six (58%) relapsed during the follow-up period (range 1.63-86.5 months). Twelve (19%) and 50 (81%) patients were allocated into group A and B, respectively. A significantly different median relapse-free survival was observed between the 2 groups (22.18 vs 42.85 months, $p = 0.0296$). Among of all genes tested, those with the higher "weight" in determining different prognosis were CD44, ALCAM, DTX2, HSPA9, CCNA2, PDX1, MYST1, COL1A1 and ABCG2. This analysis supports the idea that, other than stage,

biological variables, such as expression levels of colon cancer stem cell genes, may be relevant in determining an increased risk of relapse in resected colorectal cancer patients.

[771]

TÍTULO / TITLE: - Histone deacetylase inhibition in the treatment of acute myeloid leukemia: the effects of valproic acid on leukemic cells, and the clinical and experimental evidence for combining valproic acid with other antileukemic agents.

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

REVISTA / JOURNAL: - Clin Epigenetics. 2013 Jul 30;5(1):12. doi: 10.1186/1868-7083-5-12.

●● Enlace al texto completo (gratis o de pago) [1186/1868-7083-5-12](#)

AUTORES / AUTHORS: - Fredly H; Gjertsen BT; Bruserud O

INSTITUCIÓN / INSTITUTION: - Section for Hematology, Institute of Medicine, University of Bergen, N-5021, Bergen, Norway. hanne.fredly@med.uib.no.

RESUMEN / SUMMARY: - Several new therapeutic strategies are now considered for acute myeloid leukemia (AML) patients unfit for intensive chemotherapy, including modulation of protein lysine acetylation through inhibition of histone deacetylases (HDACs). These enzymes alter the acetylation of several proteins, including histones and transcription factors, as well as several other proteins directly involved in the regulation of cell proliferation, differentiation and apoptosis. Valproic acid (VPA) is a HDAC inhibitor that has been investigated in several clinical AML studies, usually in combination with all-trans retinoic acid (ATRA) for treatment of patients unfit for intensive chemotherapy, for example older patients, and many of these patients have relapsed or primary resistant leukemia. The toxicity of VPA in these patients is low and complete hematological remission lasting for several months has been reported for a few patients (<5% of included patients), but increased peripheral blood platelet counts are seen for 30 to 40% of patients and may last for up to 1 to 2 years. We review the biological effects of VPA on human AML cells, the results from clinical studies of VPA in the treatment of AML and the evidence for combining VPA with new targeted therapy. However, it should be emphasized that VPA has not been investigated in randomized clinical studies. Despite this lack of randomized studies, we conclude that disease-stabilizing treatment including VPA should be considered especially in unfit patients, because the possibility of improving normal blood values has been documented in several studies and the risk of clinically relevant toxicity is minimal.

[772]

TÍTULO / TITLE: - Forkhead box transcription factor 1 expression in gastric cancer: FOXM1 is a poor prognostic factor and mediates resistance to docetaxel.

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

REVISTA / JOURNAL: - J Transl Med. 2013 Sep 3;11(1):204.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-204](#)

AUTORES / AUTHORS: - Li X; Qiu W; Liu B; Yao R; Liu S; Yao Y; Liang J

RESUMEN / SUMMARY: - BACKGROUND: Forkhead box transcription factor 1 (FOXM1) has been reported to overexpress and correlate with pathogenesis in a variety of human malignancies. However, little research has been done to investigate its clinical significance in gastric cancer. METHODS: We examined the expression of FOXM1 in 103 postoperational gastric cancer tissues and 5 gastric cell lines by immunohistochemistry and western blot analysis respectively. Data on clinic-pathological features and relevant prognostic factors in these patients were then analyzed. Moreover, the association of FOXM1 expression and chemosensitivity to docetaxel in gastric cancer cells was further explored. RESULTS: Our study demonstrated that the level of FOXM1 expression was significantly higher in gastric cancer than in para-cancer tissues ($P < 0.001$) and normal gastric cell lines ($P = 0.026$). No significant association was found between FOXM1 expression and any clinical pathological features ($P > 0.1$). FOXM1 amplification was identified as an independent prognostic factor in gastric cancer ($P = 0.001$), and its affection is more significant in patients with tumor size larger than 5 cm ($P = 0.004$), pT3-4 ($P = 0.003$) or pIII-IV ($P = 0.001$). Additionally, shown to mediate docetaxel resistance in gastric cancers by our research, FOXM1 was revealed to alter microtubule dynamics in response to the treatment of docetaxel, and the drug resistance could be reversed with FOXM1 inhibitor thiothrepton treatment. CONCLUSIONS: FOXM1 can be a useful marker for predicting patients' prognosis and monitoring docetaxel response, and might be a new therapeutic target in docetaxel resistant gastric cancer.

[773]

TÍTULO / TITLE: - The epidermal growth factor receptor-tyrosine kinase inhibitor era has changed the causes of death of patients with advanced non-small-cell lung cancer.

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

REVISTA / JOURNAL: - J Chin Med Assoc. 2013 Sep 21. pii: S1726-4901(13)00204-9. doi: 10.1016/j.jcma.2013.08.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.jcma.2013.08.006](#)

AUTORES / AUTHORS: - Wu WS; Chen YM; Tsai CM; Shih JF; Lee YC; Perng RP; Whang-Peng J

INSTITUCIÓN / INSTITUTION: - Department of Chest Medicine, Taipei Veterans General Hospital, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC.

RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective against tumor EGFR-mutated non-small cell lung cancer (NSCLC). Patients with the tumor EGFR-activating mutation (EGFRmu) had superior survival, compared to patients with EGFR wild-type tumors (EGFRwt). Many patients with the EGFRmu have had disease progression with EGFR-TKI treatment because of central nervous system (CNS) metastases. The objective of this

retrospective study was to compare the causes of death in patients with a known tumor EGFR mutation status who had been treated with EGFR-TKIs. METHODS: We retrospectively reviewed the chart records of our patients with advanced NSCLC who had received diagnosis, treatment, and supportive and hospice care in our hospital between July 2005 and June 2010. The tumor EGFR mutation status was analyzed by using a DNA sequence method. All enrolled patients had a documented cause of death. RESULTS: Ninety-four patients had documented tumor EGFR data, had received EGFR-TKI treatment (either erlotinib or gefitinib), and were with or without previous or salvage systemic chemotherapy. Of the 94 patients, 36 patients had EGFRwt and 58 patients had EGFRmu. The overall patient survival after starting EGFR-TKI treatment was significantly longer in the EGFRmu patients (median 17.2 months) than in the EGFRwt patients (median 11.6 months; $p = 0.0058$). Twenty-nine patients died of CNS metastases and 65 died of organ failure (other than the CNS). Patients who died of CNS metastases had undergone EGFR-TKI treatment significantly longer than patients who died of other organ failure (median, 8 months vs. 1.9 months; $p = 0.0003$) with a hazard ratio of 2.308 [95% confidence interval (C.I.), 1.452-3.668; $p = 0.0004$]. A significantly higher proportion of EGFRmu patients (26 of 58 patients; 44.8%) than EGFRwt patients (3 of 36 patients; 8.3%) ($p < 0.001$) died of CNS metastases. CONCLUSION: The EGFRmu NSCLC patients survived longer and had a significantly higher probability of mortality due to CNS metastases, compared to the EGFRwt patients. This change in the causes of death was noted after the era of EGFR-TKI treatment, and will have an important impact on the strategies and management of supportive and hospice care for patients.

[774]

TÍTULO / TITLE: - XRCC3 Thr241Met Polymorphism and Clinical Outcomes of NSCLC Patients Receiving Platinum-Based Chemotherapy: A Systematic Review and Meta-Analysis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e69553. doi: 10.1371/journal.pone.0069553. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0069553

AUTORES / AUTHORS: - Shen XY; Lu FZ; Wu Y; Zhao LT; Lin ZF

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, The Huadong Hospital, Shanghai Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - INTRODUCTION: X-ray repair cross-complementing protein 3 (XRCC3) is an essential gene involved in the double-strand break repair pathway. Published evidence has shown controversial results about the relationship between XRCC3 Thr241Met polymorphism and clinical outcomes of non-small cell lung cancer (NSCLC) patients receiving platinum-based chemotherapy. METHODS: A systematic

review and meta-analysis was performed to evaluate the predictive value of XRCC3 Thr241Met polymorphism on clinical outcomes of advanced NSCLC receiving platinum-based chemotherapy. Response to chemotherapy, overall survival (OS) and progression-free survival (PFS) were analyzed. RESULTS: A number of 11 eligible studies were identified according to the inclusion criteria. Carriers of the variant XRCC3 241Met allele were significantly associated with good response to platinum-based chemotherapy (ThrMet/MetMet vs. ThrThr: OR = 1.509, 95% CI: 1.099-2.072, Pheterogeneity = 0.618). The XRCC3 Thr241Met polymorphism was not associated with OS (MetMet vs. ThrThr, HR = 0.939, 95% CI:0.651-1.356, Pheterogeneity = 0.112) or PFS (MetMet vs. ThrThr, HR = 0.960, 95% CI: 0.539-1.710, Pheterogeneity = 0.198). Additionally, no evidence of publication bias was observed. CONCLUSIONS: This systematic review and meta-analysis shows that carriers of the XRCC3 241Met allele are associated with good response to platinum-based chemotherapy in advanced NSCLC, while the XRCC3 Thr241Met polymorphism is not associated with OS or PFS.

[775]

TÍTULO / TITLE: - Lapatinib sensitivities of two novel trastuzumab-resistant HER2 gene-amplified gastric cancer cell lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Gastric Cancer. 2013 Aug 15.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10120-013-0290-6](#)

AUTORES / AUTHORS: - Oshima Y; Tanaka H; Murakami H; Ito Y; Furuya T; Kondo E; Kodera Y; Nakanishi H

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterological Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Trastuzumab (Tmab) resistance is a major clinical problem to be resolved in patients with HER2-positive gastric cancers. However, in contrast to the situation for HER2-positive breast cancer lines, the Tmab-resistant gastric cancer preclinical models that are needed to develop a new therapy to overcome this problem are not yet available. METHODS: We developed three new cell lines from HER2 gene-amplified gastric cancer cell lines (GLM-1, GLM-4, NCI N-87) by a new in vivo selection method consisting of the repeated culture of small residual peritoneal metastasis but not subcutaneous tumor after Tmab treatment. We then evaluated the anti-tumor efficacy of lapatinib for these Tmab-resistant cells. RESULTS: We successfully isolated two Tmab-resistant cell lines (GLM1-HerR2(3), GLM4-HerR2) among the three tested cell lines. These resistant cells differed from the parental cells in their flat morphology and rapid growth in vitro, but HER2, P95HER2 expression, and Tmab binding were essentially the same for the parental and resistant cells. MUC4 expression was up- or downregulated depending on the cell line. These resistant cells were still sensitive to lapatinib, similar to the parental cells, in vitro. This growth inhibition of the Tmab-resistant cells by lapatinib was due to both G1 cell-cycle arrest

and apoptosis induction via effective blockade of the PI3K/Akt and MAPK pathways. A preclinical study confirmed that the Tmab-resistant tumors are significantly susceptible to lapatinib. CONCLUSION: These results suggest that lapatinib has antitumor activity against the Tmab-resistant gastric cancer cell lines, and that these cell lines are useful for understanding the mechanism of Tmab resistance and for developing a new molecular therapy for Tmab-resistant HER2-positive gastric cancers.

[776]

TÍTULO / TITLE: - The prognostic value of Her4 receptor isoform expression in triple-negative and Her2 positive breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 24;13(1):437.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-437](#)

AUTORES / AUTHORS: - Machleidt A; Buchholz S; Diermeier-Daucher S; Zeman F; Ortmann O; Brockhoff G

RESUMEN / SUMMARY: - BACKGROUND: Not only four but rather seven different human epidermal growth factor receptor related (Her) receptor tyrosine kinases (RTKs) have been described to be expressed in a variety of normal and neoplastic tissues: Her1, Her2, Her3, and additionally four Her4 isoforms have been identified. A differential expression of Her4 isoforms does not, however, play any role in either the molecular diagnostics or treatment decision for breast cancer patients. The prognostic and predictive impact of Her4 expression in breast cancer is basically unclear. METHODS: We quantified the Her4 variants JM-a/CYT1, JM-a/CYT2, JM-b/CYT1, and JM-b/CYT2 by isoform-specific polymerase chain reaction (qPCR) in (i) triple-negative, (ii) Her2 positive breast cancer tissues and (iii) in benign breast tissues. RESULTS: In all three tissue collectives we never found the JM-b/CYT1 or the JM-b/CYT2 isoform expressed. In contrast, the two JM-a/CYT1 and JM-a/CYT2 isoforms were always simultaneously expressed but at different ratios. We identified a positive prognostic impact on overall survival (OS) in triple-negative and event-free survival (EFS) in Her2 positive patients. This finding is independent of the absolute JM-a/CYT1 to JM-a/CYT2 expression ratio. In Her2 positive patients, Her4 expression only has a favorable effect in estrogen-receptor (ER)-positive but not in ER-negative individuals. CONCLUSION: In summary, JM-a/CYT1 and JM-a/CYT2 but not JM-b isoforms of the Her4 receptor are simultaneously expressed in both triple-negative and Her2 positive breast cancer tissues. Although different expression ratios of the two JM-a isoforms did not reveal any additional information, Her4 expression basically indicates a prolonged EFS and OFS. An extended expression analysis that takes all Her receptor homologs, including the Her4 isoforms, into account might render more precisely the molecular diagnostics required for the development of optimized targeted therapies.

[777]

TÍTULO / TITLE: - Predictive Value of BRCA1, ERCC1, ATP7B, PKM2, TOPOI, TOPOmicron-IIA, TOPOIIB and C-MYC Genes in Patients with Small Cell Lung Cancer (SCLC) Who Received First Line Therapy with Cisplatin and Etoposide.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 13;8(9):e74611. doi: 10.1371/journal.pone.0074611.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074611](#)

AUTORES / AUTHORS: - Karachaliou N; Papadaki C; Lagoudaki E; Trypaki M; Sfakianaki M; Koutsopoulos A; Mavroudis D; Stathopoulos E; Georgoulas V; Souglakos J

INSTITUCIÓN / INSTITUTION: - Laboratory of Tumour Cell Biology, School of Medicine, University of Crete, Heraklion, Crete, Greece ; Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece.

RESUMEN / SUMMARY: - BACKGROUND: The aim of the study was to evaluate the predictive value of genes involved in the action of cisplatin-etoposide in Small Cell Lung Cancer (SCLC). METHODS: 184 SCLC patients' primary tumour samples were analyzed for ERCC1, BRCA1, ATP7B, PKM2 TOPOI, TOPOIIA, TOPOIIB and C-MYC mRNA expression. All patients were treated with cisplatin-etoposide. RESULTS: The patients' median age was 63 years and 120 (65%) had extended stage, 75 (41%) had increased LDH serum levels and 131 (71%) an ECOG performance status was 0-1. Patients with limited stage, whose tumours expressed high ERCC1 ($p=0.028$), PKM2 ($p=0.046$), TOPOI ($p=0.008$), TOPOIIA ($p=0.002$) and TOPOIIB ($p<0.001$) mRNA had a shorter Progression Free Survival (PFS). In limited stage patients, high expression of ERCC1 ($p=0.014$), PKM2 ($p=0.026$), TOPOIIA ($p=0.021$) and TOPOIIB ($p=0.019$) was correlated with decreased median overall survival (mOS) while in patients with extended stage, only high TOPOIIB expression had a negative impact on Os ($p=0.035$). The favorable expression signature expression signature (low expression of ERCC1, PKM2, TOPOIIA and TOPOIIB) was correlated with significantly better PFS and Os in both LS-SCLC ($p<0.001$ and $p=0.007$, respectively) and ES-SCLC ($p=0.007$ and ($p=0.011$, respectively) group. The unfavorable expression signature was an independent predictor for poor PFS (HR: 3.18; $p=0.002$ and HR: 3.14; $p=0.021$) and Os (HR: 4.35; $p=0.001$ and HR: 3.32; $p=0.019$) in both limited and extended stage, respectively. CONCLUSIONS: Single gene's expression analysis as well as the integrated analysis of ERCC1, PKM2, TOPOIIA and TOPOIIB may predict treatment outcome in patients with SCLC. These findings should be further validated in a prospective study.

[778]

TÍTULO / TITLE: - Neurological and cytological response as potential early predictors of time-to-progression and overall survival in patients with leptomeningeal carcinomatosis treated with intrathecal liposomal cytarabine: a retrospective cohort study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Neurooncol. 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1007/s11060-013-1241-0](#)

AUTORES / AUTHORS: - Fusco JP; Castanon E; Carranza OE; Zubiri L; Martin P; Espinos J; Rodriguez J; Santisteban M; Aramendia JM; Gil-Bazo I

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Clinica Universidad de Navarra, c/Pio XII 36, 31008, Pamplona, España.

RESUMEN / SUMMARY: - Interesting neurological and cytological response rates after intrathecal (i.t) liposomal cytarabine have been observed in patients with leptomeningeal carcinomatosis (LMC) from solid tumors. However, the potential use of those responses as early predictors of time-to-progression (TTP) and overall survival (OS) is unexplored. 27 consecutive patients with LMC treated with 50 mg i.t liposomal cytarabine under compassionate drug use were retrospectively studied. All patients received i.t treatment every 2 weeks during induction and every 4 weeks during maintenance periods. Neurological and cytological responses were assessed before every liposomal cytarabine cycle. Most of the patients were female (17/27) diagnosed with breast cancer (15/27). A complete neurological response was seen among 11 % of the patients; partial response in 22 % of the patients; stable disease in 30 % of the patients and progressive disease in 37 % of them. Cytological assessment was available in 11/27 patients showing a 26 % complete response rate. The median time to neurological and cytological response was 15 days and 14 days, respectively. Patients showing a combined neurological and cytological response showed a significantly longer median TTP (122 vs. 3 days; $p = 0.001$) and OS (141 vs. 3 days; $p = 0.002$) compared to those showing both neurological and cytological progression. No grade 4 toxicities were recorded. According to these preliminary results, early neurological and cytological responses may be further studied as early predictors of TTP and OS in patients receiving i.t liposomal cytarabine for LMC.

[779]

TÍTULO / TITLE: - IGF-1 receptor and IGF binding protein-3 might predict prognosis of patients with resectable pancreatic cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Aug 21;13(1):392. doi: 10.1186/1471-2407-13-392.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-392](#)

AUTORES / AUTHORS: - Hirakawa T; Yashiro M; Murata A; Hirata K; Kimura K; Amano R; Yamada N; Nakata B; Hirakawa K

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Osaka, Abeno-ku, Japan.
m9312510@med.osaka-cu.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: The present study aimed to elucidate the clinicopathologic role of insulin-like growth factor-1 receptor (IGF1R) and IGF binding protein-3 (IGFBP3) in patients with pancreatic cancer. The function of IGFBP3 is controversial, because both inhibition and facilitation of the action of IGF as well as IGF-independent effects have been reported. In this study, IGF1R and IGFBP3 expression was examined, and their potential roles as prognostic markers in patients with pancreatic cancer were evaluated. METHODS: Clinicopathological features of 122 patients with curatively resected pancreatic cancer were retrospectively reviewed, and expression of IGF1R and IGFBP3 was immunohistochemically analyzed. RESULTS: Expression of IGF1R and IGFBP3 was observed in 50 (41.0%) and 37 (30.3%) patients, respectively. IGF1R expression was significantly associated with histological grade ($p = 0.037$). IGFBP3 expression had a significant association with tumor location ($p = 0.023$), and a significant inverse association with venous invasion ($p = 0.037$). Tumors with IGF1R-positive and IGFBP3-negative expression ($n = 32$) were significantly frequently Stage II and III ($p = 0.011$). The prognosis for IGF1R positive patients was significantly poorer than that for IGF1R negative patients ($p = 0.0181$). IGFBP3 protein expression did not correlate significantly with patient survival. The subset of patients with both positive IGF1R and negative IGFBP3 had worse overall survival (8.8 months versus 12.6 months, respectively, $p < 0.001$). CONCLUSION: IGF1R signaling might be associated with tumor aggressiveness, and IGFBP3 might show antiproliferative effects in pancreatic cancer. Both high IGF1R expression and low IGFBP3 expression represent useful prognostic markers for patients with curatively resected pancreatic cancer.

[780]

TÍTULO / TITLE: - Influence of CYP3A4 genotypes in the outcome of serous ovarian cancer patients treated with first-line chemotherapy: implication of a CYP3A4 activity profile.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Clin Exp Med. 2013 Aug 1;6(7):552-61. Print 2013.

AUTORES / AUTHORS: - Assis J; Pereira D; Gomes M; Marques D; Marques I; Nogueira A; Catarino R; Medeiros R

INSTITUCIÓN / INSTITUTION: - Molecular Oncology Group-CI, Portuguese Institute of Oncology Porto, Portugal ; Research Department, Portuguese League against Cancer (NRNorte) Porto, Portugal.

RESUMEN / SUMMARY: - CYP3A4 is a key enzyme involved in the metabolism of numerous compounds, such as paclitaxel, and its activity shows an extensive inter-individual variation which can influence treatment response. The study's purpose was to investigate the potential predictive role of a CYP3A4 profile (CYP3A4*1B, rs2740574 and CYP3A4*22, rs35599367) in serous ovarian cancer patients treated with first-line chemotherapy (paclitaxel and cisplatin or carboplatin), after cytoreductive surgery. CYP3A4*1B and CYP3A4*22 genotypes were determined by Nested PCR-RFLP and

Taqman® Allelic Discrimination, respectively. We observed that the mean survival rates were statistically different according the patients CYP3A4 genotypes. The group of patients carrying the CYP3A4*1B G allele present a decreased mean survival rate when compared with AA genotype patients (103.93 and 134.44 months, respectively, $p = 0.010$). This result is consistent after multivariate Cox regression analysis (HR, 2.15; 95% CI, 1.03-4.52; $p = 0.043$). The combination of CYP3A4*1B and CYP3A4*22 polymorphisms result in the definition of a CYP3A4 activity profile: the group of patients with a higher CYP3A4 activity profile had significantly diminished survival when compared with patients with a lower CYP3A4 activity profile (101.06 and 134.44 months, respectively, $p = 0.012$). Multivariate Cox regression analysis revealed a diminished overall survival time for patients with CYP3A4 high activity profile (HR, 2.29; 95% CI, 1.05-5.02; $p = 0.038$). The definition of a CYP3A4 activity profile resulted in the increase of prediction ability, using Harrel's concordance indexes (C-index from 0.617 to 0.626). To conclude, our results demonstrate an association between CYP3A4*1B and a diminished overall survival of patients with serous ovarian cancer. The definition of a CYP3A4 activity profile proved to be benefic and the CYP3A4 high activity profile was associated with a lower overall survival. We consider that the definition of a CYP3A4 activity profile might be useful as molecular marker for predicting the clinical outcome of serous ovarian cancer patients.

[781]

TÍTULO / TITLE: - Influence of a patient information program on adherence and persistence with an aromatase inhibitor in breast cancer treatment - the COMPAS study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 4;13(1):407.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-407](#)

AUTORES / AUTHORS: - Ziller V; Kyvernitakis I; Knoll D; Storch A; Hars O; Hadji P

RESUMEN / SUMMARY: - BACKGROUND: It is known that suboptimal adherence rates may affect endocrine treatments for breast cancer, but little information has been reported whether any efforts to improve treatment adherence have been successful. We designed a randomized, controlled study to investigate the effect of oral or written patient information program on adherence and persistence when receiving an aromatase inhibitor (AI). METHODS: The study cohort included 181 female patients receiving an adjuvant AI treatment randomly assigned to one of three groups The first group received reminder letters and information booklets, the second group was reminded and informed through telephone calls and the control group received neither. The primary endpoint was the rate at which patients were classified as adhering to treatment after twelve months. RESULTS: Baseline results showed a well-balanced randomization with no significant differences between groups. After 12 months, 48% (CI 35--62) of the control group, 62.7% (CI 49--75) in the telephone group

and 64.7% (CI 51--77) in the letter group were adhering to therapy. A post hoc pooled analysis with a one-way hypothesis for both interventions versus control indicated a significant difference between the groups favouring the intervention ($p = 0.039$).
CONCLUSION: The aim of this study was to investigate the efficacy of a simple and practical interventional program in enhancing adherence to breast cancer treatment. Patients receiving additional/supplemental information appeared to have an improved adherence rate even though the differences between groups were not statistically significant for the primary endpoint.

[782]

TÍTULO / TITLE: - MRI in the evaluation of breast cancer patient response to neoadjuvant chemotherapy: predictive factors for breast conservative surgery.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Diagn Interv Radiol. 2013 Sep 13. doi: 10.5152/dir.2013.13201.

●● [Enlace al texto completo \(gratis o de pago\) 5152/dir.2013.13201](#)

AUTORES / AUTHORS: - Nadrljanski MM; Milosevic ZC; Plesinac-Karapandzic V; Maksimovic R

INSTITUCIÓN / INSTITUTION: - Department of Diagnostic Imaging, Clinic of Radiation Oncology and Radiology, Institute of Oncology and Radiology of Serbia, Belgrade, Serbia.

RESUMEN / SUMMARY: - PURPOSE: We aimed to prospectively assess the role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the evaluation of predictive factors for breast conservative surgery during neoadjuvant chemotherapy. MATERIALS AND METHODS: Sixty-six patients were evaluated before the first treatment cycle, after the second cycle, and upon the completion of neoadjuvant chemotherapy according to largest tumor diameter, tumor volume, postcontrast enhancement, and tumor regression pattern. The patients were divided into responders (pathologic complete and near complete response) and nonresponders. Each subgroup was re-evaluated according to morphokinetic criteria for identification of candidates for breast conservative surgery. RESULTS: In responders ($n=27$), the lesion size upon the completion of neoadjuvant chemotherapy was significantly smaller compared to nonresponders (1.5 ± 0.6 vs. 3.2 ± 0.9 cm; $P < 0.001$), as was the volume (1.2 vs. 11.0 cm³; $P < 0.001$). The measured lesion size did not differ from the histologic size (1.5 ± 0.6 vs. 1.2 ± 0.6 cm; $P = 0.09$) and had the high correlation ($r=0.93$). In responders, the following parameters were significantly different before and after neoadjuvant chemotherapy: size (3.6 ± 1.4 to 1.5 ± 0.6 cm; $P < 0.001$), volume (17.6 to 1.2 cm³; $P < 0.001$), predominant concentric regression, plateau and continuous time-intensity curves ($P < 0.001$). DCE-MRI has the sensitivity of 87% and the accuracy of 77% to identify candidates for breast conservative surgery. CONCLUSION: Selected morphokinetic DCE-MRI parameters may contribute to the

multidisciplinary decision when considering the selection of candidates for breast conservative surgery.

[783]

TÍTULO / TITLE: - The Addition of All-Trans Retinoic Acid to Chemotherapy May Not Improve the Outcome of Patient with NPM1 Mutated Acute Myeloid Leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Oncol. 2013 Sep 6;3:218. doi: 10.3389/fonc.2013.00218.

●● Enlace al texto completo (gratis o de pago) [3389/fonc.2013.00218](#)

AUTORES / AUTHORS: - Nazha A; Bueso-Ramos C; Estey E; Faderl S; O'Brien S; Fernandez MH; Nguyen M; Koller C; Freireich E; Beran M; Pierce S; Keating M; Kantarjian H; Ravandi F

INSTITUCIÓN / INSTITUTION: - Department of Leukemia, University of Texas , Austin, TX , USA.

RESUMEN / SUMMARY: - Background: Previous studies have suggested that NPM1 mutations may be a marker for response to all-trans retinoic acid (ATRA) given as an adjunct to intensive chemotherapy in older patients with acute myeloid leukemia (AML). Patients and Methods: We examined the impact of the addition of ATRA among patients with diploid cytogenetics treated on a randomized phase II study of fludarabine + cytarabine + idarubicine +/- G-CSF +/- ATRA with available data on their NPM1 mutation status. Between September 1995 and November 1997, 215 patients were enrolled in the study. Among them, 70 patients had diploid cytogenetic and are the subjects of this analysis. Results: The median age of the 70 patients was 66 years (range 23-87). Twenty (29%) of patients had NPM1 mutations. Among them 7 (35%) did and 13 (65%) did not receive ATRA in combination with chemotherapy. Complete remission (CR) was achieved in 71% of patients treated with ATRA as compared to 69% without ATRA (P = 0.62). With median follow-up of 12.5 years, the overall survival (OS), event-free survival (EFS), and relapse-free survival (RFS) were similar among patients who received ATRA compared to no ATRA regardless of NPM1 mutation status. Conclusion: The addition of ATRA to intensive chemotherapy did not affect the overall outcome of patients with AML regardless of NPM1 mutation status.

[784]

TÍTULO / TITLE: - Correction: Granulocyte-macrophage stimulating factor (GM-CSF) increases circulating dendritic cells but does not abrogate suppression of adaptive cellular immunity in patients with metastatic colorectal cancer receiving chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Aug 15;13(1):80. doi: 10.1186/1475-2867-13-80.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-80](#)

AUTORES / AUTHORS: - Martinez M; Ono N; Planutiene M; Planutis K; Nelson EL; Holcombe RF

INSTITUCIÓN / INSTITUTION: - Tisch Cancer Institute of Mt, Sinai School of Medicine, New York, NY, USA. randall.holcombe@mssm.edu.

[785]

TÍTULO / TITLE: - Thymidylate Synthase Gene Polymorphism and Survival of Colorectal Cancer Patients Receiving Adjuvant 5-Fluorouracil.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genet Test Mol Biomarkers. 2013 Aug 22.

●● [Enlace al texto completo \(gratis o de pago\) 1089/gtmb.2013.0171](#)

AUTORES / AUTHORS: - Sulzyc-Bielicka V; Bielicki D; Binczak-Kuleta A; Kaczmarczyk M; Pioch W; Machoy-Mokrzynska A; Ciechanowicz A; Golebiewska M; Drozdziak M

INSTITUCIÓN / INSTITUTION: - 1 Department of Oncology, Pomeranian Medical University, Szczecin, Poland.

RESUMEN / SUMMARY: - Limited studies indicate a possible association of 5'-UTR thymidylate synthase enhancer region polymorphism and treatment outcome in patients medicated with 5-fluorouracil (5-FU). The study was designed to verify the relationship in patients with colorectal cancer (CRC), a Polish population that received 5-FU-based adjuvant chemotherapy. The study analyzed 145 Astler-Coller B2 and C CRC patients. Genotyping for a variable number of tandem repeats and G to C single-nucleotide polymorphism in the 5'-UTR of the thymidylate synthase (TS) gene was carried out. TS genotypes were classified into high expression (high TS) and low expression types (low TS). High TS was found in 22.8% of patients. The right-side tumors were more frequently associated with high TS than the left-side tumors ($p=0.024$). High TS was only found in 9.3% of rectal tumors, but in 29.7% of colon cancers ($p=0.0042$). Disease-free survival after 20 months (DFS 20) was longer in subjects with low TS than in high TS ($p=0.043$). Patients who underwent chemotherapy had longer DFS 20 in the low TS than in the high TS subgroup ($p=0.051$). The low TS was found to be an independent good prognostic factor for DFS 20 in the whole group as well as in the subgroup treated with chemotherapy ($p=0.024$ and $p=0.034$, respectively). Patients with low TS did not show any differences in DFS 20 whether they were treated with adjuvant chemotherapy or not. Proximal CRC tumors are characterized by higher TS expression genotypes than distal tumors, and are at significantly greater risk of early recurrence during the first 20 months after surgery.

[786]

TÍTULO / TITLE: - The combination of arsenic, interferon-alpha, and zidovudine restores an "immunocompetent-like" cytokine expression profile in patients with adult T-cell leukemia lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Retrovirology. 2013 Aug 20;10(1):91. doi: 10.1186/1742-4690-10-91.

●● Enlace al texto completo (gratis o de pago) [1186/1742-4690-10-91](https://doi.org/10.1186/1742-4690-10-91)

AUTORES / AUTHORS: - Kchour G; Rezaee SR; Farid R; Ghantous A; Rafatpanah H; Tarhini M; Kooshyar MM; El Hajj H; Berry F; Mortada M; Nasser R; Shirdel A; Dassouki Z; Ezzedine M; Rahimi H; Ghavamzadeh A; de The H; Hermine O; Mahmoudi M; Bazarbachi A

INSTITUCIÓN / INSTITUTION: - Immunology Research Centre Bu-Ali Research Institute, Mashhad University of Medical Sciences, Mashhad, Iran. MahmoudiM@mums.ac.ir.

RESUMEN / SUMMARY: - BACKGROUND: HTLV-I associated adult T-cell leukemia/lymphoma (ATL) carries a dismal prognosis due to chemo-resistance and immuno-compromised micro-environment. The combination of zidovudine and interferon-alpha (IFN) significantly improved survival in ATL. Promising results were reported by adding arsenic trioxide to zidovudine and IFN. RESULTS: Here we assessed Th1/Th2/Treg cytokine gene expression profiles in 16 ATL patients before and 30 days after treatment with arsenic/IFN/zidovudine, in comparison with HTLV-I healthy carriers and sero-negative blood donors. ATL patients at diagnosis displayed a Treg/Th2 cytokine profile with significantly elevated transcript levels of Foxp3, interleukin-10 (IL-10), and IL-4 and had a reduced Th1 profile evidenced by decreased transcript levels of interferon-gamma (IFN-gamma) and IL-2. Most patients (15/16) responded, with CD4+CD25+ cells significantly decreasing after therapy, paralleled by decreases in Foxp3 transcript. Importantly, arsenic/IFN/zidovudine therapy sharply diminished IL-10 transcript and serum levels concomitant with decrease in IL-4 and increases in IFN-gamma and IL-2 mRNA, whether or not values were adjusted to the percentage of CD4+CD25+ cells. Finally, IL-10 transcript level negatively correlated with clinical response at Day 30. CONCLUSIONS: The observed shift from a Treg/Th2 phenotype before treatment toward a Th1 phenotype after treatment with arsenic/IFN/zidovudine may play an important role in restoring an immuno-competent micro-environment, which enhances the eradication of ATL cells and the prevention of opportunistic infections.

[787]

TÍTULO / TITLE: - The combination of valproic acid, all-trans retinoic acid and low-dose cytarabine as disease-stabilizing treatment in acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Epigenetics. 2013 Aug 1;5(1):13.

●● Enlace al texto completo (gratis o de pago) [1186/1868-7083-5-13](https://doi.org/10.1186/1868-7083-5-13)

AUTORES / AUTHORS: - Fredly H; Ersvaer E; Kittang AO; Tsykunova G; Gjertsen BT; Bruserud O

RESUMEN / SUMMARY: - BACKGROUND: A large proportion of patients with acute myeloid leukemia (AML) are not fit for intensive and potentially curative therapy due

to advanced age or comorbidity. Previous studies have demonstrated that a subset of these patients can benefit from disease-stabilizing therapy based on all-trans retinoic acid (ATRA) and valproic acid. Even though complete hematological remission is only achieved for exceptional patients, a relatively large subset of patients respond to this treatment with stabilization of normal peripheral blood cell counts. METHODS: In this clinical study we investigated the efficiency and safety of combining (i) continuous administration of valproic acid with (ii) intermittent oral ATRA treatment (21.5 mg/m² twice daily) for 14 days and low-dose cytarabine (10 mg/m² daily) for 10 days administered subcutaneously. If cytarabine could not control hyperleukocytosis it was replaced by hydroxyurea or 6-mercaptopurin to keep the peripheral blood blast count below 50 x 10⁹/L. RESULTS: The study included 36 AML patients (median age 77 years, range 48 to 90 years) unfit for conventional intensive chemotherapy; 11 patients responded to the treatment according to the myelodysplastic syndrome (MDS) response criteria and two of these responders achieved complete hematological remission. The most common response to treatment was increased and stabilized platelet counts. The responder patients had a median survival of 171 days (range 102 to > 574 days) and they could spend most of this time outside hospital, whereas the nonresponders had a median survival of 33 days (range 8 to 149 days). The valproic acid serum levels did not differ between responder and nonresponder patients and the treatment was associated with a decrease in the level of circulating regulatory T cells. CONCLUSION: Treatment with continuous valproic acid and intermittent ATRA plus low-dose cytarabine has a low frequency of side effects and complete hematological remission is seen for a small minority of patients. However, disease stabilization is seen for a subset of AML patients unfit for conventional intensive chemotherapy.

[788]

TÍTULO / TITLE: - Elderly age is not a negative predictive factor for virological response to therapy with pegylated interferon-alpha and ribavirin in chronic hepatitis C virus patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Liver Int. 2013 Jul 24. doi: 10.1111/liv.12279.

●● Enlace al texto completo (gratis o de pago) [1111/liv.12279](#)

AUTORES / AUTHORS: - Frei P; Leucht AK; Held U; Kofmehl R; Manser CN; Schmitt J; Mertens J; Rau M; Baur K; Gerlach T; Negro F; Heim M; Moradpour D; Cerny A; Dufour JF; Mullhaupt B; Geier A

INSTITUCIÓN / INSTITUTION: - Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland.

RESUMEN / SUMMARY: - BACKGROUND & AIMS: Age is frequently discussed as negative host factor to achieve a sustained virological response (SVR) to antiviral therapy of chronic hepatitis C. However, elderly patients often show advanced fibrosis/cirrhosis

as known negative predictive factor. The aim of this study was to assess age as an independent predictive factor during antiviral therapy. METHODS: Overall, 516 hepatitis C patients were treated with pegylated interferon-alpha and ribavirin, thereof 66 patients ≥ 60 years. We analysed the impact of host factors (age, gender, fibrosis, haemoglobin, previous hepatitis C treatment) and viral factors (genotype, viral load) on SVR per therapy course by performing a generalized estimating equations (GEE) regression modelling, a matched pair analysis and a classification tree analysis. RESULTS: Overall, SVR per therapy course was 42.9 and 26.1%, respectively, in young and elderly patients with hepatitis C virus (HCV) genotypes 1/4/6. The corresponding figures for HCV genotypes 2/3 were 74.4 and 84%. In the GEE model, age had no significant influence on achieving SVR. In matched pair analysis, SVR was not different in young and elderly patients (54.2 and 55.9% respectively; $P = 0.795$ in binominal test). In classification tree analysis, age was not a relevant splitting variable. CONCLUSIONS: Age is not a significant predictive factor for achieving SVR, when relevant confounders are taken into account. As life expectancy in Western Europe at age 60 is more than 20 years, it is reasonable to treat chronic hepatitis C in selected elderly patients with relevant fibrosis or cirrhosis but without major concomitant diseases, as SVR improves survival and reduces carcinogenesis.

[789]

TÍTULO / TITLE: - Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Geriatr Oncol. 2013 Jul;4(3):218-26. doi: 10.1016/j.jgo.2013.04.001. Epub 2013 Apr 30.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.jgo.2013.04.001](#)

AUTORES / AUTHORS: - Aaldriks AA; van der Geest LG; Giltay EJ; le Cessie S; Portielje JE; Tanis BC; Nortier JW; Maartense E

INSTITUCIÓN / INSTITUTION: - Institute of Mental Health, Bouman GGZ Rotterdam, The Netherlands. Electronic address: a.aaldriks@telfort.nl.

RESUMEN / SUMMARY: - INTRODUCTION: In general, geriatric assessment (GA) provides the combined information on comorbidity and functional, nutritional and psychosocial status and may be predictive for mortality outcome of cancer patients. The impact of geriatric assessment on the outcome of older patients with colorectal cancer treated with chemotherapy is largely unknown. METHODS: In a prospective study, 143 patients with colorectal cancer who were 70 years and older were assessed before chemotherapy by Mini Nutritional Assessment (MNA), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Groningen Frailty Indicator (GFI) and Mini Mental State Examination (MMSE). RESULTS: Fifty-four (38%) patients received adjuvant chemotherapy and 89 (62%) patients received palliative chemotherapy. Malnutrition and frailty were prevalent in 39 (27%, assessed by MNA) and 34 (24%, by

GFI) patients, respectively; whereas cognitive impairment was prevalent in 19 (13%, by IQCODE) and 11 (8%, by MMSE) patients, respectively. In patients with palliative chemotherapy, poor MNA scores were associated with receiving less than 4 cycles of chemotherapy ($p=0.008$). Poor MNA and GFI scores were associated with increased hazard ratios (HR) for mortality for patients with palliative chemotherapy: $HR=2.76$ (95% confidence interval [CI]: 1.60-4.77; $p<0.001$) and $HR=2.72$ (95% CI: 1.58-4.69; $p<0.001$), respectively, after adjustment for several clinical parameters. CONCLUSIONS: Malnutrition and frailty were strongly associated with an increased mortality risk in patients who underwent palliative chemotherapy. Furthermore, a poor score on MNA was predictive for less tolerance of chemotherapy. Our findings may help the oncologist in future decision making and advice for elderly patients with colorectal cancer.

[790]

TÍTULO / TITLE: - Weighing the evidence for immune therapy and targeted therapy in renal cancer and melanoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncology (Williston Park). 2013 Jul;27(7):691-2, 694.

AUTORES / AUTHORS: - Dorff TB

INSTITUCIÓN / INSTITUTION: - University of Southern California Keck School of Medicine, Los Angeles, California, USA.

[791]

TÍTULO / TITLE: - Clinical Benefit From Pemetrexed Before and After Crizotinib Exposure and From Crizotinib Before and After Pemetrexed Exposure in Patients With Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lung Cancer. 2013 Aug 6. pii: S1525-7304(13)00133-2. doi: 10.1016/j.clc.2013.06.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.clc.2013.06.005](https://doi.org/10.1016/j.clc.2013.06.005)

AUTORES / AUTHORS: - Berge EM; Lu X; Maxson D; Baron AE; Gadgeel SM; Solomon BJ; Doebele RC; Varella-Garcia M; Camidge DR

INSTITUCIÓN / INSTITUTION: - Division of Medical Oncology, University of Colorado, Aurora, CO. Electronic address: Famon.Berge@ucdenver.edu.

RESUMEN / SUMMARY: - BACKGROUND: Crizotinib produces high response rates and prolonged PFS in ALK+ NSCLC. Retrospective analyses suggest enhanced sensitivity to pemetrexed in crizotinib naive ALK+ NSCLC. Cross-resistance between crizotinib and pemetrexed has not been previously investigated. PATIENTS AND METHODS: Patients with stage IV ALK+ NSCLC treated with PEM-CRIZ, or CRIZ-PEM were identified. Overall PFS and PFS excluding central nervous system events (eCNS) were compared. RESULTS: Objective response rates in evaluable patients were 66% (PEM-CRIZ) and 75% (CRIZ-

PEM) for pemetrexed and 84% (CRIZ-PEM) and 66% (PEM-CRIZ) for crizotinib. For PEM-CRIZ (n = 29), median PFS and eCNS PFS were both 6 months with pemetrexed, and 10 and 14.5 months, respectively, with crizotinib. For CRIZ-PEM (n = 9), median PFS and eCNS PFS were 4.5 and 3 months, respectively, with pemetrexed, and 8.5 and 7.5 months, respectively, with crizotinib. There was a statistically significant increase in the risk of an overall PFS event with pemetrexed when administered after crizotinib (P = .0277; hazard ratio [HR], 2.5898; 95% confidence interval [CI], 1.1100-6.0424), but differences in the risk of an eCNS PFS event were not significant (P = 0.4913; HR, 1.3521; 95% CI, 0.5727-3.1920). Neither overall nor eCNS PFS for patients while taking crizotinib was associated with a sequence effect relative to pemetrexed. CONCLUSION: Crizotinib and pemetrexed are active drugs in ALK+ NSCLC. PFS benefit appeared higher with crizotinib than with pemetrexed. PFS benefit from pemetrexed was less after crizotinib compared with before crizotinib, however, this difference was only statistically significant for overall and not eCNS PFS. Pemetrexed exposure did not seem to affect crizotinib outcomes.

[792]

TÍTULO / TITLE: - O-GlcNAcylation-inducing treatments inhibit estrogen receptor alpha expression and confer resistance to 4-OH-tamoxifen in human breast cancer-derived MCF-7 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 11;8(7):e69150. doi: 10.1371/journal.pone.0069150. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069150](https://doi.org/10.1371/journal.pone.0069150)

AUTORES / AUTHORS: - Kanwal S; Fardini Y; Pagesy P; N'tumba-Byn T; Pierre-Eugene C; Masson E; Hampe C

INSTITUCIÓN / INSTITUTION: - Institut Cochin, Université Paris Descartes, CNRS (UMR8104), Paris, France ; INSERM, U1016, Paris, France.

RESUMEN / SUMMARY: - O-GlcNAcylation (addition of N-acetyl-glucosamine on serine or threonine residues) is a post-translational modification that regulates stability, activity or localization of cytosolic and nuclear proteins. O-linked N-acetylglucosamine transferase (OGT) uses UDP-GlcNAc, produced in the hexosamine biosynthetic pathway to O-GlcNAcylate proteins. Removal of O-GlcNAc from proteins is catalyzed by the beta-N-Acetylglucosaminidase (OGA). Recent evidences suggest that O-GlcNAcylation may affect the growth of cancer cells. However, the consequences of O-GlcNAcylation on anti-cancer therapy have not been evaluated. In this work, we studied the effects of O-GlcNAcylation on tamoxifen-induced cell death in the breast cancer-derived MCF-7 cells. Treatments that increase O-GlcNAcylation (PUGNAc and/or glucosamine) protected MCF-7 cells from death induced by tamoxifen. In contrast, inhibition of OGT expression by siRNA potentiated the effect of tamoxifen on cell death. Since the PI-3 kinase/Akt pathway is a major regulator of cell survival, we

used BRET to evaluate the effect of PUGNAc+glucosamine on PIP3 production. We observed that these treatments stimulated PIP3 production in MCF-7 cells. This effect was associated with an increase in Akt phosphorylation. However, the PI-3 kinase inhibitor LY294002, which abolished the effect of PUGNAc+glucosamine on Akt phosphorylation, did not impair the protective effects of PUGNAc+glucosamine against tamoxifen-induced cell death. These results suggest that the protective effects of O-GlcNAcylation are independent of the PI-3 kinase/Akt pathway. As tamoxifen sensitivity depends on the estrogen receptor (ERalpha) expression level, we evaluated the effect of PUGNAc+glucosamine on the expression of this receptor. We observed that O-GlcNAcylation-inducing treatment significantly reduced the expression of ERalpha mRNA and protein, suggesting a potential mechanism for the decreased tamoxifen sensitivity induced by these treatments. Therefore, our results suggest that inhibition of O-GlcNAcylation may constitute an interesting approach to improve the sensitivity of breast cancer to anti-estrogen therapy.

[793]

TÍTULO / TITLE: - Evaluation of the clinical value of the newly identified urine biomarker HIST1H4K for diagnosis and prognosis of prostate cancer in Bulgarian patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J BUON. 2013 Jul-Sep;18(3):660-8.

AUTORES / AUTHORS: - Kachakova D; Mitkova A; Popov E; Beltcheva O; Vlahova A; Dikov T; Hristova S; Mitev V; Slavov C; Kaneva R

INSTITUCIÓN / INSTITUTION: - Department of Medical Chemistry and Biochemistry and Molecular Medicine Center, Medical University-Sofia, Sofia, Bulgaria.

RESUMEN / SUMMARY: - Purpose: Searching for diagnostic and prognostic biomarkers for prostate cancer (PC) is main public health priority. DNA methylation in body fluids is a stable, easily detectable and promising PC biomarker. The major advantages of urine-based assays are their noninvasive nature and the ability to monitor PC with heterogeneous foci. The aim of this study was to determine the diagnostic value of the recently identified candidate PC biomarker HIST1H4K. Methods: We investigated DNA methylation of HIST1H4K in urine samples from 57 PC patients, 29 controls with benign prostatic hyperplasia (BPH) and 50 young asymptomatic men (YAM) by MethyLight real-time PCR. Results: The frequency of HIST1H4K promoter hypermethylation significantly discriminated PC patients from YAM (AUC =0.763; 95% CI 0.672-0.839; $p < 0.0001$), but did not show any statistical difference between PC patients and BPH controls (AUC=0.513, 95% CI 0.402-0.622; $p = 0.8255$). HIST1H4K could not outperform the prostatic specific antigen (PSA) in our sample (AUC=0.785; 95% CI 0.679-0.870; $p < 0.0001$). Methylation of HIST1H4K showed significant correlation with aging ($r = 0.5418$; $p < 0.0001$), but with no other clinicopathological characteristics. Conclusion: The results suggest that the promoter hypermethylation of HIST1H4K is rather due to

aging than related to prostate carcinogenesis. To elucidate this observation analysis of larger samples is needed.

[794]

TÍTULO / TITLE: - Poor Outcome of Patients With Myelodysplastic Syndrome After Azacitidine Treatment Failure.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Sep 17. pii: S2152-2650(13)00249-8. doi: 10.1016/j.clml.2013.07.007.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clml.2013.07.007](#)

AUTORES / AUTHORS: - Duong VH; Lin K; Reljic T; Kumar A; Al Ali NH; Lancet JE; List AF; Komrokji RS

INSTITUCIÓN / INSTITUTION: - University of Maryland Greenebaum Cancer Center, Baltimore, MD.

RESUMEN / SUMMARY: - BACKGROUND: Limited data have been reported describing the outcome and prognosis of patients with MDS in whom treatment with azanucleosides has failed. We report our single-institutional experience of patients with higher-risk MDS in whom therapy with azacitidine has failed. PATIENTS AND METHODS: This was a retrospective study of MDS patients treated at the Moffitt Cancer Center in whom azacitidine treatment regimens had failed. Patients were identified through the Moffitt database, and clinical data were extracted. Azacitidine failure was defined as failure to achieve hematologic improvement or better after at least 4 cycles of therapy, loss of response, or disease progression during therapy. The objectives were to characterize response to salvage therapies after azacitidine failure and to estimate the overall survival. All responses were defined according to the International Working Group 2006 criteria, and survival was estimated using the Kaplan-Meier method. RESULTS: A total of 59 patients in whom azacitidine treatment had failed were identified. The median age at treatment failure was 68 years, and most were Caucasian male patients. Thirteen patients received intensive chemotherapy with an overall response rate of 31%. Six patients were treated with decitabine, and none responded. Median overall survival of the entire cohort after azacitidine failure was 5.8 months (95% confidence interval, 1.3-10.3 months), with an estimated 12-month survival of 17%. CONCLUSION: Patients with higher-risk MDS in whom azacitidine treatment has failed have a poor prognosis and low probability of response to salvage treatments. The standard of care after azanucleoside failure should be enrollment in clinical trials.

[795]

TÍTULO / TITLE: - Pharmacogenetics of ABC and SLC transporters in metastatic colorectal cancer patients receiving first-line FOLFIRI treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenet Genomics. 2013 Oct;23(10):549-57. doi: 10.1097/FPC.0b013e328364b6cf.

●● Enlace al texto completo (gratis o de pago) [1097/FPC.0b013e328364b6cf](https://doi.org/10.1097/FPC.0b013e328364b6cf)

AUTORES / AUTHORS: - De Mattia E; Toffoli G; Polesel J; D'Andrea M; Corona G; Zagonel V; Buonadonna A; Dreussi E; Cecchin E

INSTITUCIÓN / INSTITUTION: - aExperimental and Clinical Pharmacology Unit
bEpidemiology and Biostatistics Unit cMedical Oncology Unit, 'Centro di Riferimento Oncologico' - National Cancer Institute, Aviano dMedical Oncology Unit, 'San Filippo Neri Hospital', Rome eMedical Oncology Unit 1, Istituto Oncologico Veneto - IRCCS, Padova, Italy.

RESUMEN / SUMMARY: - **OBJECTIVE:** Membrane transporters are widely recognized as important determinants of drug disposition and response, generating increasing interest on the pharmacological implications of their genetic variations. The aim of this study was to elucidate the predictive/prognostic role of ATP-binding cassette (ABC) and solute carrier (SLC) protein polymorphisms on irinotecan (FOLFIRI regimen) outcome. **PATIENTS AND METHODS:** A total of 250 White metastatic colorectal cancer patients homogeneously treated with a first-line FOLFIRI regimen were genotyped for a panel of variants in five transporter genes. The primary study endpoints were the response rate (partial or complete response), overall survival, and time to progression. Toxicity was considered a secondary endpoint. Irinotecan pharmacokinetic data of 71 patients were used for polymorphism functional analysis. **RESULTS:** Two variants of the ABCG2 (-15622C>T, rs7699188) gene were found to be predictive (P<0.01) of the response rate. High-order relationships of ABC/SLC markers with previously investigated genetic (UGT1A1 polymorphisms) and nongenetic (primary tumor site) factors that helped determine the response rate were highlighted. A prognostic effect of the ABCB1 rs2032582 variant on patient overall survival emerged (P=0.0074). The ABCG2 rs7699788 variant was also seen to be associated with grade 3-4 nonhematological toxicity (P=0.0012). The ABCG2 (-15622C>T, rs7699188) and ABCB1 (rs2032582) polymorphisms were not found to be associated with pharmacokinetic parameters. **CONCLUSION:** This study showed that ABC/SLC polymorphisms have a crucial contribution toward the FOLFIRI outcome. This could represent a further step toward personalized therapy.

[796]

TÍTULO / TITLE: - Predictive value of ERCC1 and RRM1 gene single-nucleotide polymorphisms for first-line platinum- and gemcitabine-based chemotherapy in non-small cell lung cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Rep. 2013 Nov;30(5):2385-98. doi: 10.3892/or.2013.2696. Epub 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2696](https://doi.org/10.3892/or.2013.2696)

AUTORES / AUTHORS: - Mlak R; Krawczyk P; Ramlau R; Kalinka-Warzocho E; Wasylecka-Morawiec M; Wojas-Krawczyk K; Kucharczyk T; Homa I; Koziol P; Ciesielka M; Chudziak D; Milanowski J

INSTITUCIÓN / INSTITUTION: - Department of Pneumology, Oncology and Allergology, Medical University of Lublin, 20-954 Lublin, Poland.

RESUMEN / SUMMARY: - Platinum-based chemotherapy with third generation drugs (such as gemcitabine) is an efficacious regimen of first-line treatment of patients with advanced, unresectable non-small cell lung cancer (NSCLC), without activating EGFR mutations. Mechanism of action of cytostatics are distortions in the DNA. ERCC1 and RRM1 are key proteins involved in the repair of DNA, thus, they may be responsible for the ineffectiveness of therapy. We investigated whether ERCC1 (19007C>T) and RRM1 (-37C>A) polymorphisms impact response to chemotherapy and survival in 62 patients with NSCLC treated with platinum and gemcitabine. Single nucleotide polymorphisms (SNPs) were assessed using a PCR-RFLP method in DNA isolated from PBLs. There were no statistically significant relationships between ERCC1 genotypes and response to therapy ($p=0.581$, $\chi^2=1.09$) as well as patient overall survival (OS). Carriers of the RRM1 AC genotype showed disease progression significantly more frequently ($p=0.019$, $\chi^2=5.473$) compared to carriers of the AA or CC genotypes. Carriers of the ERCC1/RRM1TT/CC genotype combination showed disease control significantly more frequently ($p=0.047$, $\chi^2=3.95$) compared to carriers of other genotype combinations. Patients with AA or CC genotypes of RRM1 showed significantly higher progression-free survival probability ($p=0.0001$, HR=0.39, 95% CI, 0.22-0.70) and OS probability ($p=0.0104$, HR=0.39, 95% CI, 0.18-0.82) compared to those with the AC genotype. In Cox regression model, poor performance status ($p=0.0016$, HR=4.78, 95% CI, 1.82-12.56), AC genotype of RRM1 gene ($p=0.0414$, HR=2.47, 95% CI, 1.04-5.87), lack of prior surgical treatment ($p=0.0425$, HR=4.71, 95% CI, 1.06-20.92) and lack of subsequent lines of treatment ($p=0.0127$, HR=3.23, 95% CI, 1.29-8.11) were significantly associated with shortening of patient survival. The analysis of RRM1 (-37C>A) more than ERCC1 (19007C>T) polymorphism may be a promising tool in the qualification of NSCLC patients for chemotherapy containing platinum compounds and gemcitabine.

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[797]

TÍTULO / TITLE: - The G-Protein Coupled Estrogen Receptor (GPER/GPR30) is a Gonadotropin Receptor Dependent Positive Prognosticator in Ovarian Carcinoma Patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e71791. doi: 10.1371/journal.pone.0071791.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071791](https://doi.org/10.1371/journal.pone.0071791)

AUTORES / AUTHORS: - Heublein S; Mayr D; Vrekoussis T; Friese K; Hofmann SS; Jeschke U; Lenhard M

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynaecology, Campus Innenstadt, Ludwig-Maximilians-University of Munich, Munich, Germany.

RESUMEN / SUMMARY: - Follicle stimulating hormone receptor (FSHR) and luteinizing hormone receptor (LHCGR) were demonstrated to impact upon survival of patients suffering from epithelial ovarian cancer (EOC). Though structure wise the G-protein coupled estrogen receptor (GPER/GPR30) is related to FSHR/LHCGR, its prognostic impact in EOC remains controversial. We recently found that FSHR negative patients represent a specific EOC subgroup that may behave differently in respect to both treatment response and prognosis. Hence, the current study aimed to analyze how GPER may interact with the FSHR/LHCGR system in EOC and whether the prognostic significance of GPER in EOC cases (n = 151) may be dependent on the FSHR/LHCGR immunophenotype of the tumor. Ovarian cancer cell lines were used to study how FSH and LH regulate GPER and whether GPER activation differentially affects in vitro cell proliferation in presence/absence of activated FSHR/LHCGR. In EOC tissue, GPER correlated with FSHR/LHCGR and was related to prolonged overall survival only in FSHR/LHCGR negative patients. Although GPER was found to be specifically induced by LH/FSH, GPER agonists (4-Hydroxy-Tamoxifen, G1) reduced EOC cell proliferation only in case of LH/FSH unstimulated pathways. To the same direction, only patients characterized as LHCGR/FSHR negative seem to gain from GPER in terms of survival. Our combined tissue and in vitro results support thus the hypothesis that GPER activation could be of therapeutic benefit in LHCGR/FSHR negative EOC patients. Further studies are needed to evaluate the impact of GPER activation on a clinical scheme.

[798]

TÍTULO / TITLE: - Flavopiridol synergizes with sorafenib to induce cytotoxicity and potentiate antitumorigenic activity in EGFR/HER-2 and mutant RAS/RAF breast cancer model systems.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neoplasia. 2013 Aug;15(8):939-51.

AUTORES / AUTHORS: - Nagaria TS; Williams JL; Leduc C; Squire JA; Greer PA; Sangrar W

INSTITUCIÓN / INSTITUTION: - Division of Cancer Biology and Genetics, Queen's Cancer Research Institute, Queen's University, Kingston, Ontario, Canada.

RESUMEN / SUMMARY: - Oncogenic receptor tyrosine kinase (RTK) signaling through the Ras-Raf-Mek-Erk (Ras-MAPK) pathway is implicated in a wide array of carcinomas, including those of the breast. The cyclin-dependent kinases (CDKs) are implicated in regulating proliferative and survival signaling downstream of this pathway. Here, we show that CDK inhibitors exhibit an order of magnitude greater cytotoxic potency than a suite of inhibitors targeting RTK and Ras-MAPK signaling in cell lines representative of

clinically recognized breast cancer (BC) subtypes. Drug combination studies show that the pan-CDK inhibitor, flavopiridol (FPD), synergistically potentiated cytotoxicity induced by the Raf inhibitor, sorafenib (SFN). This synergy was most pronounced at sub-EC50 SFN concentrations in MDA-MB-231 (KRAS-G13D and BRAF-G464V mutations), MDA-MB-468 [epidermal growth factor receptor (EGFR) overexpression], and SKBR3 [ErbB2/EGFR2 (HER-2) overexpression] cells but not in hormone-dependent MCF-7 and T47D cells. Potentiation of SFN cytotoxicity by FPD correlated with enhanced apoptosis, suppression of retinoblastoma (Rb) signaling, and reduced Mcl-1 expression. SFN and FPD were also tested in an MDA-MB-231 mammary fat pad engraftment model of tumorigenesis. Mice treated with both drugs exhibited reduced primary tumor growth rates and metastatic tumor load in the lungs compared to treatment with either drug alone, and this correlated with greater reductions in Rb signaling and Mcl-1 expression in resected tumors. These findings support the development of CDK and Raf co-targeting strategies in EGFR/HER-2-overexpressing or RAS/RAF mutant BCs.

[799]

TÍTULO / TITLE: - The cancer testis antigen NXF2 is activated by the hypomethylating agent decitabine in acute leukemia cells in vitro and in vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Nov;8(5):1549-1555. doi: 10.3892/mmr.2013.1659. Epub 2013 Aug 28.

●● [Enlace al texto completo \(gratis o de pago\) 3892/mmr.2013.1659](#)

AUTORES / AUTHORS: - Zhou J; Li Y; Yao Y; Wang L; Gao L; Gao X; Luo X; Li J; Jiang M; Zhou M; Wang L; Yu L

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Chinese People's Liberation Army General Hospital, Beijing 100853, P.R. China.

RESUMEN / SUMMARY: - Cancer testis antigens (CTAs) are a group of tumor-associated antigens restricted to male germ cells under normal physiological conditions. CTAs are expressed in certain types of tumors and thus are a novel target for immunotherapy. Nuclear RNA export factor 2 (NXF2) is a CTA of which the expression pattern, regulation and clinical significance are unclear. In the present study, following treatment with a demethylating agent, decitabine, NXF2 expression was detected in the majority of the NXF2-negative acute leukemia cell lines, but not in healthy donor samples. This finding was confirmed by western blot analysis. Eight primary acute leukemia bone marrow samples were treated with decitabine in vitro, and results showed that NXF2 expression was significantly upregulated. In another nine acute myeloid leukemia or myelodysplastic syndrome patients, it was noted that the expression of NXF2 was upregulated in all patients following the first cycle of decitabine, which suggested that NXF2 was activated by decitabine treatment in vivo.

Furthermore, NXF2 expression in acute leukemia cells was demonstrated to be regulated by CpG island hypermethylation. To the best of our knowledge, this is the first study to demonstrate that NXF2 is activated by demethylation in acute leukemia cells in vitro and in vivo. NXF2 may therefore serve as a novel target for immunotherapy against acute leukemia.

[800]

TÍTULO / TITLE: - Predictive value of serum bone sialoprotein and prostate-specific antigen doubling time in patients with bone metastasis of prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Huazhong Univ Sci Technolog Med Sci. 2013 Aug;33(4):559-62. doi: 10.1007/s11596-013-1158-z. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1007/s11596-013-1158-z](#)

AUTORES / AUTHORS: - Wang Y; Zhang XF; Dai J; Zheng YC; Zhang MG; He JJ

INSTITUCIÓN / INSTITUTION: - The Medical Laboratory, Dujiangyan People's Hospital, Dujiangyan, 611830, China, 625971522@qq.com.

RESUMEN / SUMMARY: - This study aimed to evaluate the diagnostic and prognostic significance of serum bone sialoprotein (BSP) and prostate-specific antigen doubling time (PSADT) in patients with bone metastasis (BM) from prostate cancer (PC). A total of 116 patients with PC, 120 patients with benign prostatic hyperplasia (BPH) and 120 healthy controls were enrolled in this study. PC patients were divided into bone metastasis (BM) group (n=56) and non-bone metastasis (NBM) group (n=60). Serum BSP was detected by Sandwich ELISA. Severity of bone pain was evaluated using visual analogue score (VAS). Serum f-PSA and t-PSA levels were measured by using electrochemiluminescence immunoassay (ECLIA). PSADT was calculated according to the formula: $PSADT = \lg(2) / [\log(PSA2) - \log(PSA1)]$. The mean serum BSP level in PC patients with BM was significantly higher than in PC patients without BM, BPH patients and controls ($P < 0.001$ for all). Pearson's analysis showed that serum BSP level was positively correlated with VAS in PC patients with BM ($P < 0.05$). Receiver operating characteristics (ROC) analysis demonstrated that BSP discriminated patients with BM from those without BM at the cutoff value of 33.26 ng/mL. The sensitivity and specificity were 78.21% and 79.28%, respectively. The optimal cutoff value of PSADT was 131 days, with sensitivity of 85.69% and specificity of 85.36%. Kaplan-Meier analysis revealed that subjects with higher BSP levels/shorter PSADT had a shorter BM-free period than those with lower BSP levels/longer PSADT. Serum BSP and PSADT are useful biomarkers for the diagnosis of BM from PC, and can be regarded as independent factors for predicting the prognosis of BM from PC. Combined determination of BSP and PSADT can improve accuracy and positive rate of BM from PC significantly.

[801]

TÍTULO / TITLE: - Androgen receptor phosphorylation at serine 308 and serine 791 predicts enhanced survival in castrate resistant prostate cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Aug 13;14(8):16656-71. doi: 10.3390/ijms140816656.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140816656](#)

AUTORES / AUTHORS: - McCall P; Adams CE; Willder JM; Bennett L; Qayyum T; Orange C; Underwood MA; Edwards J

INSTITUCIÓN / INSTITUTION: - Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK.

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RESUMEN / SUMMARY: - We previously reported that AR phosphorylation at serine 213 was associated with poor outcome and may contribute to prostate cancer development and progression. This study investigates if specific AR phosphorylation sites have differing roles in the progression of hormone naive prostate cancer (HNPC) to castrate resistant disease (CRPC). A panel of phosphospecific antibodies were employed to study AR phosphorylation in 84 matched HNPC and CRPC tumours. Immunohistochemistry measured Androgen receptor expression phosphorylated at serine residues 94 (pAR94), 308 (pAR308), 650(pAR650) and 791 (pAR791). No correlations with clinical parameters were observed for pAR94 or pAR650 in HNPC or CRPC tumours. In contrast to our previous observation with serine 213, high pAR308 is significantly associated with a longer time to disease specific death ($p = 0.011$) and high pAR791 expression significantly associated with a longer time to disease recurrence ($p = 0.018$) in HNPC tumours and longer time to death from disease recurrence ($p = 0.040$) in CRPC tumours. This observation in CRPC tumours was attenuated in high apoptotic tumours ($p = 0.022$) and low proliferating tumours ($p = 0.004$). These results demonstrate that understanding the differing roles of AR phosphorylation is necessary before this can be exploited as a target for castrate resistant prostate cancer.

[802]

TÍTULO / TITLE: - Upregulated expression of C-X-C chemokine receptor 4 is an independent prognostic predictor for patients with gastric cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 6;8(8):e71864. doi: 10.1371/journal.pone.0071864. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071864](#)

AUTORES / AUTHORS: - He H; Wang C; Shen Z; Fang Y; Wang X; Chen W; Liu F; Qin X; Sun Y

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China.

RESUMEN / SUMMARY: - Aberrant chemokine (C-X-C motif) receptor CXCR4 expressions in malignant tissues have been reported, but its role in gastric cancer prognosis remains unknown. Our studies were designed to investigate the expression and prognostic significance of CXCR4 in patients with gastric cancer. CXCR4 expression was retrospectively analyzed by immunohistochemistry in 97 patients with gastric adenocarcinoma from China. Results were assessed for association with clinical features and overall survival by using Kaplan-Meier analysis. Prognostic values of CXCR4 expression and clinical outcomes were evaluated by Cox regression analysis. A molecular prognostic stratification scheme incorporating CXCR4 expression was determined by using receiver operating characteristic (ROC) analysis. The results show that CXCR4 predominantly localized in the cell membranes and cytoplasm. The protein level of CXCR4 was upregulation in gastric cancer tissues and upregulated expression of CXCR4 was only significantly associated with Lauren classification ($P < 0.001$). Increased CXCR4 expression in gastric cancer tissues was positively correlated with poor overall survival of gastric cancer patients ($P < 0.001$). Further multivariate Cox regression analysis suggested that intratumoral CXCR4 expression was an independent prognostic indicator for the disease. Applying the prognostic value of intratumoral CXCR4 density to TNM stage system showed a better prognostic value in patients with gastric cancer. In conclusion, intratumoral CXCR4 expression was recognized as an independent prognostic marker for the overall survival of patients with gastric cancer. On the basis of TNM stage, detection of CXCR4 expression will be helpful for predicting prognosis for patients with gastric cancer.

[803]

TÍTULO / TITLE: - Histone deacetylase inhibitors restore toxic BH3 domain protein expression in anoikis resistant mammary and brain cancer stem cells thereby enhancing the response to anti-ERBB1/ERBB2 therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Aug 22;14(10).

AUTORES / AUTHORS: - Cruickshanks N; Hamed HA; Booth L; Tavallai S; Syed J; Sajithlal GB; Grant S; Poklepovic A; Dent P

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery; Virginia Commonwealth University; Richmond, VA USA.

[804]

TÍTULO / TITLE: - Targeting proliferating cell nuclear antigen and its protein interactions induces apoptosis in multiple myeloma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 31;8(7):e70430. doi: 10.1371/journal.pone.0070430. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0070430

AUTORES / AUTHORS: - Muller R; Misund K; Holien T; Bachke S; Gilljam KM; Vatsveen TK; Ro TB; Bellacchio E; Sundan A; Otterlei M

INSTITUCIÓN / INSTITUTION: - Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

RESUMEN / SUMMARY: - Multiple myeloma is a hematological cancer that is considered incurable despite advances in treatment strategy during the last decade. Therapies targeting single pathways are unlikely to succeed due to the heterogeneous nature of the malignancy. Proliferating cell nuclear antigen (PCNA) is a multifunctional protein essential for DNA replication and repair that is often overexpressed in cancer cells. Many proteins involved in the cellular stress response interact with PCNA through the five amino acid sequence AlkB homologue 2 PCNA-interacting motif (APIM). Thus inhibiting PCNA's protein interactions may be a good strategy to target multiple pathways simultaneously. We initially found that overexpression of peptides containing the APIM sequence increases the sensitivity of cancer cells to contemporary therapeutics. Here we have designed a cell-penetrating APIM-containing peptide, ATX-101, that targets PCNA and show that it has anti-myeloma activity. We found that ATX-101 induced apoptosis in multiple myeloma cell lines and primary cancer cells, while bone marrow stromal cells and primary healthy lymphocytes were much less sensitive. ATX-101-induced apoptosis was caspase-dependent and cell cycle phase-independent. ATX-101 also increased multiple myeloma cells' sensitivity against melphalan, a DNA damaging agent commonly used for treatment of multiple myeloma. In a xenograft mouse model, ATX-101 was well tolerated and increased the anti-tumor activity of melphalan. Therefore, targeting PCNA by ATX-101 may be a novel strategy in multiple myeloma treatment.

TÍTULO / TITLE: - Rebma200, a humanized monoclonal antibody targeting the sodium phosphate transporter NaPi2b displays strong immune mediated cytotoxicity against cancer: a novel reagent for targeted antibody therapy of cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 31;8(7):e70332. doi: 10.1371/journal.pone.0070332. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0070332

AUTORES / AUTHORS: - Lopes dos Santos M; Yeda FP; Tsuruta LR; Horta BB; Pimenta AA Jr; Degaki TL; Soares IC; Tuma MC; Okamoto OK; Alves VA; Old LJ; Ritter G; Moro AM

INSTITUCIÓN / INSTITUTION: - Lab. de Biofarmacos em Celulas Animais, Instituto Butantan, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - NaPi2b, a sodium-dependent phosphate transporter, is highly expressed in ovarian carcinomas and is recognized by the murine monoclonal

antibody MX35. The antibody had shown excellent targeting to ovarian cancer in several early phase clinical trials but being murine the antibody's full therapeutic potential could not be explored. To overcome this impediment we developed a humanized antibody version named Rebmab200, expressed in human PER.C6® cells and cloned by limiting dilution. In order to select a clone with high therapeutic potential clones were characterized using a series of physicochemical assays, flow cytometry, real-time surface plasmon resonance, glycosylation analyses, immunohistochemistry, antibody-dependent cell-mediated cytotoxicity, complement-dependent-cytotoxicity assays and quantitative PCR. Comparative analyses of Rebmab200 and MX35 monoclonal antibodies demonstrated that the two antibodies had similar specificity for NaPi2b by flow cytometry with a panel of 30 cell lines and maintained similar kinetic parameters. Robust and high producer cell clones potentially suitable for use in manufacturing were obtained. Rebmab200 antibodies were assessed by immunohistochemistry using a large panel of tissues including human carcinomas of ovarian, lung, kidney and breast origin. An assessment of its binding towards 33 normal human organs was performed as well. Rebmab200 showed selected strong reactivity with the tested tumor types but little or no reactivity with the normal tissues tested confirming its potential for targeted therapeutics strategies. The remarkable cytotoxicity shown by Rebmab200 in OVCAR-3 cells is a significant addition to the traits of stability and productivity displayed by the top clones of Rebmab200. Antibody-dependent cell-mediated toxicity functionality was confirmed in repeated assays using cancer cell lines derived from ovary, kidney and lung as targets. To explore use of this antibody in clinical trials, GMP production of Rebmab200 has been initiated. As the next step of development, Phase I clinical trials are now planned for translation of Rebmab200 into the clinic.

[805]

TÍTULO / TITLE: - A novel class of substituted spiro [quinazoline-2,1'-cyclohexane] derivatives as effective PPAR-1 inhibitors: molecular modeling, synthesis, cytotoxic and enzyme assay evaluation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Pol Pharm. 2013 Jul-Aug;70(4):687-708.

AUTORES / AUTHORS: - Amin KM; Anwar MM; Syam YM; Khedr M; Kamel MM; Kassem EM

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Cairo University, Egypt.

RESUMEN / SUMMARY: - Molecular docking simulation study was carried out to design a novel series of spiro [(2H, 3H)quinazoline-2,1'-cyclohexan]-4(1H)-one derivatives as a new class of effective PARP-1 inhibitors. Spiro [2H-3,1-benzoxazine-2,1'-cyclohexan]-4(1H)-one (5) was the starting compound to synthesize the target proposed analogues. The derivatives that showed the top scores and had the best fitting in the binding sites

chemotherapies. The predictive meaning of EGFR mutation for chemotherapy should be further investigated.

[807]

TÍTULO / TITLE: - NK-cell-dependent killing of colon carcinoma cells is mediated by natural cytotoxicity receptors (NCRs) and stimulated by parvovirus infection of target cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 31;13:367. doi: 10.1186/1471-2407-13-367.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1471-2407-13-367](#)

AUTORES / AUTHORS: - Bhat R; Rommelaere J

INSTITUCIÓN / INSTITUTION: - German Cancer Research Center (DKFZ), Tumor Virology, F010, Im Neuenheimer Feld 242, Heidelberg D-69120, Germany. r.bhat@dkfz.de

RESUMEN / SUMMARY: - BACKGROUND: Investigating how the immune system functions during malignancies is crucial to developing novel therapeutic strategies. Natural killer (NK) cells, an important component of the innate immune system, play a vital role in immune defense against tumors and virus-infected cells. The poor survival rate in colon cancer makes it particularly important to develop novel therapeutic strategies. Oncolytic viruses, in addition to lysing tumor cells, may have the potential to augment antitumor immune responses. In the present study, we investigate the role of NK cells and how parvovirus H-1PV can modulate NK-cell mediated immune responses against colon carcinoma. METHODS: Human NK cells were isolated from the blood of healthy donors. The cytotoxicity and antibody-mediated inhibition of NK cells were measured in chromium release assays. Phenotypic assessment of colon cancer and dendritic cells was done by FACS. The statistical significance of the results was calculated with Student's t test (*p < 0.05; **, p < 0.01; ***, p < 0.001). RESULTS: We show that IL-2-activated human NK cells can effectively kill colon carcinoma cells. Killing of colon carcinoma cells by NK cells was further enhanced upon infection of the former cells with parvovirus H-1PV. H-1PV has potent oncolytic activity against various tumors, yet its direct killing effect on colon carcinoma cells is limited. The cytotoxicity of NK cells towards colon carcinoma cells, both mock- and H-1PV-infected, was found to be mostly mediated by a combination of natural cytotoxicity receptors (NCRs), namely NKp30, 44, and 46. Colon carcinoma cells displayed low to moderate expression of NK cell ligands, and this expression was modulated upon H-1PV infection. Lysates of H-1PV-infected colon carcinoma cells were found to increase MHC class II expression on dendritic cells. CONCLUSIONS: Altogether, these data suggest that IL-2-activated NK cells actively kill colon carcinoma cells and that this killing is mediated by several natural cytotoxicity receptors (NCRs) in combination. Additionally, in association with parvovirus H-1PV, IL-2-activated NK cells have the potential to boost immune responses against colon cancer.

[808]

TÍTULO / TITLE: - Serum apolipoprotein B-100 concentration predicts the virological response to pegylated interferon plus ribavirin combination therapy in patients infected with chronic hepatitis C virus genotype 1b.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Med Virol. 2013 Jul;85(7):1180-90. doi: 10.1002/jmv.23597.

●● Enlace al texto completo (gratis o de pago) [1002/jmv.23597](#)

AUTORES / AUTHORS: - Yoshizawa K; Abe H; Aida Y; Ishiguro H; Ika M; Shimada N; Tsubota A; Aizawa Y

INSTITUCIÓN / INSTITUTION: - Division of Gastroenterology and Hepatology, Department of Internal Medicine, Jikei University School of Medicine Katsushika Medical Center, Tokyo, Japan. kaiyoshiza@yahoo.co.jp

RESUMEN / SUMMARY: - Host lipoprotein metabolism is associated closely with the life cycle of hepatitis C virus (HCV), and serum lipid profiles have been linked to the response to pegylated interferon (Peg-IFN) plus ribavirin (RBV) therapy. Polymorphisms in the human IL28B gene and amino acid substitutions in the core and interferon sensitivity-determining region (ISDR) in NS5A of HCV genotype 1b (G1b) were also shown to strongly affect the outcome of Peg-IFN plus RBV therapy. In this study, an observational cohort study was performed in 247 HCV G1b-infected patients to investigate whether the response to Peg-IFN and RBV combination therapy in these patients is independently associated with the level of lipid factors, especially apolipoprotein B-100 (apoB-100), an obligatory structural component of very low density lipoprotein and low density lipoprotein. The multivariate logistic analysis subsequently identified apoB-100 (odds ratio (OR), 1.602; 95% confidence interval (CI), 1.046-2.456), alpha-fetoprotein (OR, 0.764; 95% CI, 0.610-0.958), non-wild-type ISDR (OR, 5.617; 95% CI, 1.274-24.754), and the rs8099917 major genotype (OR, 34.188; 95% CI, 10.225-114.308) as independent factors affecting rapid initial virological response (decline in HCV RNA levels by ≥ 3 -log₁₀ at week 4). While lipid factors were not independent predictors of complete early or sustained virological response, the serum apoB-100 level was an independent factor for sustained virological response in patients carrying the rs8099917 hetero/minor genotype. Together, we conclude that serum apoB-100 concentrations could predict virological response to Peg-IFN plus RBV combination therapy in patients infected with HCV G1b, especially in those with the rs8099917 hetero/minor genotype.

[809]

TÍTULO / TITLE: - Complete remission obtained with azacitidine in a patient with concomitant therapy related myeloid neoplasm and pulmonary mucormycosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mediterr J Hematol Infect Dis. 2013 Jul 10;5(1):e2013048. doi: 10.4084/MJHID.2013.048. Print 2013.

●● Enlace al texto completo (gratis o de pago) [4084/MJHID.2013.048](#)

AUTORES / AUTHORS: - Capria S; De Angelis F; Gentile G; Trisolini SM; Brocchieri S; Canichella M; Chiusolo P; Micozzi A; Foa R; Meloni G

INSTITUCIÓN / INSTITUTION: - Department of Cellular Biotechnologies and Hematology, "Sapienza" University of Rome, Rome, Italy.

RESUMEN / SUMMARY: - Mucormycosis is the third cause of invasive mycosis after candidiasis and aspergillosis in AML patients, representing a poor prognostic factor associated with a high rate of fatal outcome. We report a case of a patient with AML and a concomitant pulmonary mucormycosis at diagnosis, who obtained a complete remission both of her AML and of the fungal infection. The incidence of the infection at the onset of leukemia is extremely unusual, and, to our knowledge, the sporadic cases reported in the literature are included in heterogeneous series retrospectively examined. In our case, Liposomal Amphotericin B as single agent appeared incapable of controlling the infection, so anti-infective therapy was intensified with posaconazole and simultaneously antileukemic treatment with 5-azacitidine was started, with the understanding that the only antifungal treatment would not have been able to keep the infection under control for a long time if not associated with a reversal of neutropenia related to the disease. We observed a progressive improvement of the general conditions, a healing of pneumonia and a complete remission of the leukemic disease, suggesting that a careful utilization of the new compounds available today, in terms of both antifungal and antileukemic treatment, may offer a curative chance a patient who would have otherwise been considered unfit for a potentially curative therapeutic strategy.

[810]

TÍTULO / TITLE: - Glutathione s-transferase t1, o1 and o2 polymorphisms are associated with survival in muscle invasive bladder cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 11;8(9):e74724. doi: 10.1371/journal.pone.0074724.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074724](#)

AUTORES / AUTHORS: - Djukic TI; Savic-Radojevic AR; Pekmezovic TD; Matic MG; Pljesa-Ercegovac MS; Coric VM; Radic TM; Suvakov SR; Krivic BN; Dragicevic DP; Simic TP

INSTITUCIÓN / INSTITUTION: - Institute of Medical and Clinical Biochemistry, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

RESUMEN / SUMMARY: - **OBJECTIVE:** To examine the association of six glutathione transferase (GST) gene polymorphisms (GSTT1, GSTP1/rs1695, GSTO1/rs4925, GSTO2/rs156697, GSTM1, GSTA1/rs3957357) with the survival of patients with muscle invasive bladder cancer and the genotype modifying effect on chemotherapy. **PATIENTS AND METHODS:** A total of 105 patients with muscle invasive bladder cancer were included in the study. The follow-up lasted 5 years. The effect of GSTs

polymorphisms on predicting mortality was analyzed by the Cox proportional hazard models, while Kaplan-Meier analysis was performed to assess differences in survival. RESULTS: GSTT1 active, GSTO1 Asp140Asp or GSTO2 Asp142Asp genotypes were independent predictors of a higher risk of death among bladder cancer patients (HR = 2.5, P = 0.028; HR = 2.9, P = 0.022; HR = 3.9, P = 0.001; respectively) and significantly influenced the overall survival. There was no association between GSTP1, GSTM1 and GSTA1 gene variants with overall mortality. Only GSTO2 polymorphism showed a significant effect on the survival in the subgroup of patients who received chemotherapy (P = 0.006). CONCLUSION: GSTT1 active genotype and GSTO1 Asp140Asp and GSTO2 Asp142Asp genotypes may have a prognostic/pharmacogenomic role in patients with muscle invasive bladder cancer.

[811]

TÍTULO / TITLE: - Screening in silico predicted remotely acting NF1 gene regulatory elements for mutations in patients with neurofibromatosis type 1.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hum Genomics. 2013 Aug 15;7:18. doi: 10.1186/1479-7364-7-18.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1479-7364-7-18](#)

AUTORES / AUTHORS: - Hamby SE; Reviriego P; Cooper DN; Upadhyaya M; Chuzhanova N
INSTITUCIÓN / INSTITUTION: - School of Science and Technology, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK.

RESUMEN / SUMMARY: - Neurofibromatosis type 1 (NF1), a neuroectodermal disorder, is caused by germline mutations in the NF1 gene. NF1 affects approximately 1/3,000 individuals worldwide, with about 50% of cases representing de novo mutations. Although the NF1 gene was identified in 1990, the underlying gene mutations still remain undetected in a small but obdurate minority of NF1 patients. We postulated that in these patients, hitherto undetected pathogenic mutations might occur in regulatory elements far upstream of the NF1 gene. In an attempt to identify such remotely acting regulatory elements, we reasoned that some of them might reside within DNA sequences that (1) have the potential to interact at distance with the NF1 gene and (2) lie within a histone H3K27ac-enriched region, a characteristic of active enhancers. Combining Hi-C data, obtained by means of the chromosome conformation capture technique, with data on the location and level of histone H3K27ac enrichment upstream of the NF1 gene, we predicted in silico the presence of two remotely acting regulatory regions, located, respectively, approximately 600 kb and approximately 42 kb upstream of the NF1 gene. These regions were then sequenced in 47 NF1 patients in whom no mutations had been found in either the NF1 or SPRED1 gene regions. Five patients were found to harbour DNA sequence variants in the distal H3K27ac-enriched region. Although these variants are of uncertain pathological significance and still remain to be functionally characterized, this approach promises to be of general utility

for the detection of mutations underlying other inherited disorders that may be caused by mutations in remotely acting regulatory elements.

[812]

TÍTULO / TITLE: - Testis specific gene expression drives disease progression and Rituximab resistance in lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - EMBO Mol Med. 2013 Aug;5(8):1149-50. doi: 10.1002/emmm.201303018.

●● Enlace al texto completo (gratis o de pago) 1002/emmm.201303018

AUTORES / AUTHORS: - Knapp S

INSTITUCIÓN / INSTITUTION: - Nuffield Department of Clinical Medicine, Target Discovery Institute (TDI) and Structural Genomics Consortium (SGC), University of Oxford, Oxford, UK. stefan.knapp@sgc.ox.ac.uk

[813]

TÍTULO / TITLE: - Aberrant signalling by protein kinase CK2 in imatinib-resistant chronic myeloid leukaemia cells: Biochemical evidence and therapeutic perspectives.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Oncol. 2013 Aug 22. pii: S1574-7891(13)00117-8. doi: 10.1016/j.molonc.2013.08.006.

●● Enlace al texto completo (gratis o de pago) 1016/j.molonc.2013.08.006

AUTORES / AUTHORS: - Borgo C; Cesaro L; Salizzato V; Ruzzene M; Massimino ML; Pinna LA; Donella-Deana A

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, University of Padova and CNR Neuroscience Institute, Viale G. Colombo 3, 35131 Padova, Italy.

RESUMEN / SUMMARY: - Chronic myeloid leukaemia (CML) is driven by the fusion protein Bcr-Abl, a constitutively active tyrosine kinase playing a crucial role in initiation and maintenance of CML phenotype. Despite the great efficacy of the Bcr-Abl-specific inhibitor imatinib, resistance to this drug is recognized as a major problem in CML treatment. We found that in LAMA84 cells, characterized by imatinib-resistance caused by BCR-ABL1 gene amplification, the pro-survival protein kinase CK2 is up-regulated as compared to the sensitive cells. CK2 exhibits a higher protein-level and a parallel enhancement of catalytic activity. Consistently, CK2-catalysed phosphorylation of Akt-Ser129 is increased. CK2 co-localizes with Bcr-Abl in the cytoplasmic fraction as judged by subcellular fractionation and fluorescence immunolocalization. CK2 and Bcr-Abl are members of the same multi-protein complex(es) in imatinib-resistant cells as demonstrated by co-immunoprecipitation and co-sedimentation in glycerol gradients. Cell treatment with CX-4945, a CK2 inhibitor currently in clinical trials, counteracts CK2/Bcr-Abl interaction and causes cell death by apoptosis. Interestingly, combination of CX-4945 with imatinib displays a synergistic effect in reducing cell viability.

Consistently, knockdown of CK2alpha expression by siRNA restores the sensitivity of resistant LAMA84 cells to low imatinib concentrations. Remarkably, the CK2/Bcr-Abl interaction and the sensitization towards imatinib obtained by CK2-inhibition in LAMA84 is observable also in other imatinib-resistant CML cell lines. These results demonstrate that CK2 contributes to strengthen the imatinib-resistance phenotype of CML cells conferring survival advantage against imatinib. We suggest that CK2 inhibition might be a promising tool for combined strategies in CML therapy.

[814]

TÍTULO / TITLE: - Age, tumour stage, and preoperative serum albumin level are independent predictors of mortality after radical cystectomy for treatment of bladder cancer in Hong Kong Chinese.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hong Kong Med J. 2013 Oct;19(5):400-6. Epub 2013 Aug 8.

●● [Enlace al texto completo \(gratis o de pago\) 12809/hkmj133964](#)

AUTORES / AUTHORS: - Chan ES; Yip SK; Hou SM; Lee WM; Ng CF

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong.

RESUMEN / SUMMARY: - **OBJECTIVES.** To evaluate the association between patient age, other clinical factors and mortality following radical cystectomy for treatment of bladder cancer. **DESIGN.** Historical cohort study. **SETTING.** A urology unit in Hong Kong. **PATIENTS.** The outcomes of 117 patients who had radical cystectomies performed in one urological unit from 2003 to 2011 were reviewed. Demographic and perioperative data, including tumour stage, Charlson Comorbidity Index, and preoperative serum albumin levels were retrieved from computerised medical records. Risk factors for 30-day mortality, and cancer-specific, other-cause, and overall death rates at 5 years were calculated. The data were subsequently stratified and analysed according to age. **RESULTS.** Of the 117 patients, 83 (71%) were aged 75 years or below. The mean follow-up duration was 31 (standard deviation, 29) months. Age, tumour stage, and preoperative serum albumin level, but not the Charlson Comorbidity Index, were found to be predictors of survival following radical cystectomy. The overall 30-day mortality rate was 3% in the full sample, 1% in patients aged 75 years or below, and 10% in patients aged over 75 years. There was no significant difference in 5-year cancer-caused mortalities between patients aged 75 years or below and those aged over 75 years (33% vs 33%, P=0.956). In patients older than 75 years, the 5-year other-cause and overall mortality rates were 47% and 80%, respectively; such rates were higher than those for younger patients (13% and 46%, respectively). **CONCLUSION.** Age, tumour stage, and preoperative serum albumin level were predictors of survival after radical cystectomy. Non-cancer-related death played a crucial role in the overall mortality rate in elderly patients having radical cystectomy for bladder cancer.

[815]

TÍTULO / TITLE: - Circulating tumor cells: application as a biomarker for molecular characterization and predictor of survival in an all-comer solid tumor phase I clinical study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 21;8(8):e58557. doi: 10.1371/journal.pone.0058557.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0058557](https://doi.org/10.1371/journal.pone.0058557)

AUTORES / AUTHORS: - Bao H; Burke PA; Huang J; Chen X; Brohawn PZ; Yao Y; Lechleider RJ; Sikorski RS; Buzoianu M; Zhang J; Shi X; Richman LK; Lavalley TM

INSTITUCIÓN / INSTITUTION: - Department of Translational Sciences, MedImmune LLC, Gaithersburg, Maryland, United States of America.

RESUMEN / SUMMARY: - PURPOSE: Clinical development of cancer drugs has a low success rate. Prognostic and predictive biomarkers using minimally invasive approaches hold promise for increasing the probability of success by enabling disease characterization, patient selection and early detection of drug treatment effect. Enumeration and molecular characterization of circulating tumor cells (CTC) may address some of these needs, and thus were evaluated for utility in a Phase I solid tumor clinical study. EXPERIMENTAL DESIGN: Blood samples for CTC analysis were obtained from 24 cancer patients in a multi-center all-comer Phase I study of MEDI-575, a novel anti-PDGFRalpha antibody. Samples were taken at screening and analyzed for enumeration of CTC using the CellSearch(®) platform and for molecular characterization using a novel quantitative RT-PCR assay. RESULTS: Fifty-nine percent of the patients showed at least 1 CTC per 7.5 ml of blood at baseline. Progression-free survival (PFS) and overall survival (OS) of patients with 0 CTCs at baseline were longer than PFS and Os for patients with 1-3 and >3 CTCs (8.8 versus 1.4 and 1.3 months PFS, P = 0.02; 9.0 vs 7.4 and 3.5 months OS, P = 0.20, respectively). Patients with 0 CTC showed a greater percentage of stable disease than the other 2 groups with 1-3 and >3 CTCs (57% vs 29% and 0%). The multimarker qRT-PCR method detected CTC in 40% of the patients, and 80% of these patients were positive for pre-selected drug target genes. CONCLUSION: CTC enumeration of patients in an all-comer study is feasible and may allow for patient stratification for PFS and Os to evaluate the clinical response of investigational agents. Gene expression profiling of isolated CTC may provide a means for molecular characterization of selected tumor targets.

[816]

TÍTULO / TITLE: - Up-regulation of miR-9 expression as a poor prognostic biomarker in patients with non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Transl Oncol. 2013 Sep 10.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1106-1](https://doi.org/10.1007/s12094-013-1106-1)

AUTORES / AUTHORS: - Xu T; Liu X; Han L; Shen H; Liu L; Shu Y

INSTITUCIÓN / INSTITUTION: - Department of Oncology, the First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing, 210029, People's Republic of China.

RESUMEN / SUMMARY: - PURPOSE: Emerging evidences indicate that dysregulated microRNAs are implicated in cancer tumorigenesis and progression. MicroRNA-9 (miR-9) has various expression patterns in diverse human cancers. However, its clinical significance in human non-small cell lung cancer has not yet been elucidated. In the present study, we detected the expression of miR-9 in non-small cell lung cancer and adjacent noncancerous tissues and explored its relationships with clinicopathological characteristics and prognosis. METHODS: Expression levels of miR-9 in 116 pairs of non-small cell lung cancer and adjacent normal tissues were detected by real-time quantitative RT-PCR assay. To determine its prognostic value, overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method. Univariate and multivariate analysis were performed using the Cox proportional hazard analysis. RESULTS: MiR-9 expression in non-small cell lung cancer tissues was significantly higher than that in adjacent normal tissues ($p = 0.001$), and its up-regulation was significantly correlated to advanced tumor-node-metastasis (TNM) stage ($p < 0.001$), tumor size ($p = 0.013$), and lymph node metastasis ($p = 0.001$). Furthermore, Kaplan-Meier analysis demonstrated that high miR-9 expression clearly predicted poorer PFS ($p < 0.001$) and OS ($p < 0.001$). In the multivariate analysis, increased miR-9 expression was an independent prognostic factor for both PFS ($p = 0.002$) and OS ($p = 0.013$). CONCLUSIONS: MiR-9 was up-regulated in non-small cell lung cancer tissues and correlated with adverse clinical features and unfavorable survival, indicating that miR-9 might be involved in non-small lung cancer progression and could serve as a promising biomarker for further risk stratification in the treatment of this cancer.

[817]

TÍTULO / TITLE: - Prognostic Value of EGFR Mutation and ERCC1 in Patients with Non-Small Cell Lung Cancer Undergoing Platinum-Based Chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e71356. doi: 10.1371/journal.pone.0071356. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071356](https://doi.org/10.1371/journal.pone.0071356)

AUTORES / AUTHORS: - Yamashita F; Azuma K; Yoshida T; Yamada K; Kawahara A; Hattori S; Takeoka H; Zaizen Y; Kawayama T; Kage M; Hoshino T

INSTITUCIÓN / INSTITUTION: - Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan.

RESUMEN / SUMMARY: - BACKGROUND: In order to improve the outcome of patients with non-small cell lung cancer (NSCLC), a biomarker that can predict the efficacy of chemotherapy is needed. The aim of this study was to assess the role of EGFR mutations and ERCC1 in predicting the efficacy of platinum-based chemotherapy and the outcome of patients with NSCLC. METHODS: We conducted a retrospective study to analyze the relationships between EGFR mutations or ERCC1 expression and progression-free survival (PFS) in patients with NSCLC who received platinum-based chemotherapy. EGFR mutation status was determined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, and immunohistochemistry was used to examine the expression of ERCC1 in tumor samples obtained from the patients. RESULTS: Among the NSCLC patients who received platinum-based chemotherapy, the median PFS was significantly better in those who had never smoked and those with exon 19 deletion, and the median overall survival (OS) was significantly better in those who had never smoked, those with exon 19 deletion, and women. Cox regression analysis revealed that exon 19 deletion and having never smoked were significantly associated with both PFS and OS. Subset analysis revealed a significant correlation between ERCC1 expression and EGFR mutation, and ERCC1-negative patients with exon 19 deletion had a longer PFS than the other patients; ERCC1-positive patients without exon 19 deletion had a shorter PFS than the other patients. CONCLUSIONS: Our results indicate that among NSCLC patients receiving platinum-based chemotherapy, those with exon 19 deletion have a longer PFS and OS. Our findings suggest that platinum-based chemotherapy is more effective against ERCC1-negative and exon 19-positive NSCLC.

[818]

TÍTULO / TITLE: - First-in-human, Pharmacokinetic and Pharmacodynamic Phase I Study of Resminostat, an Oral Histone Deacetylase Inhibitor, in Patients with Advanced Solid Tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Oct 1;19(19):5494-5504. Epub 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0735](#)

AUTORES / AUTHORS: - Brunetto AT; Ang JE; Lal R; Olmos D; Molife LR; Kristeleit R; Parker A; Casamayor I; Olaleye M; Mais A; Hauns B; Strobel V; Hentsch B; de Bono JS

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Drug Development Unit, Divisions of Cancer Therapeutics & Clinical Studies, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom; and 4SC AG, Planegg-Martinsried, Germany.

RESUMEN / SUMMARY: - PURPOSE: This first-in-human dose-escalating trial investigated the safety, tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT), pharmacokinetics, and pharmacodynamics of the novel histone deacetylase (HDAC) inhibitor resminostat in patients with advanced solid tumors. EXPERIMENTAL DESIGN:

Resminostat was administered orally once-daily on days 1 to 5 every 14 days at 5 dose levels between 100 and 800 mg. Safety, pharmacokinetics, pharmacodynamics including histone acetylation and HDAC enzyme activity, and antitumor efficacy were assessed. RESULTS: Nineteen patients (median age 58 years, range 39-70) were treated. At 800 mg, 1 patient experienced grade 3 nausea and vomiting, grade 2 liver enzyme elevation, and grade 1 hypokalemia and thrombocytopenia; these were declared as a combined DLT. No other DLT was observed. Although an MTD was not reached and patients were safely dosed up to 800 mg, 3 of 7 patients treated with 800 mg underwent dose reductions after the DLT-defining period due to cumulative gastrointestinal toxicities and fatigue. All toxicities resolved following drug cessation. No grade 4 treatment-related adverse event was observed. The pharmacokinetic profile was dose-proportional with low inter-patient variability. Pharmacodynamic inhibition of HDAC enzyme was dose-dependent and reached 100% at doses ≥ 400 mg. Eleven heavily pretreated patients had stable disease and 1 patient with metastatic thymoma had a 27% reduction in target lesion dimensions. CONCLUSIONS: Resminostat was safely administered with a dose-proportional pharmacokinetic profile, optimal on-target pharmacodynamic activity at dose levels ≥ 400 mg and signs of antitumor efficacy. The recommended phase II dose is 600 mg once-daily on days 1 to 5 every 14 days. Clin Cancer Res; 19(19); 5494-504. ©2013 AACR. \$!"1096.95\$!"TATATAT - Clin Cancer Res

[819]

TÍTULO / TITLE: - Ziyuglycoside II-induced apoptosis in human gastric carcinoma BGC-823 cells by regulating Bax/Bcl-2 expression and activating caspase-3 pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Braz J Med Biol Res. 2013 Aug;46(8):670-5. doi: 10.1590/1414-431X20133050. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1590/1414-431X20133050](#)

AUTORES / AUTHORS: - Zhu AK; Zhou H; Xia JZ; Jin HC; Wang K; Yan J; Zuo JB; Zhu X; Shan T

INSTITUCIÓN / INSTITUTION: - Affiliated Hangzhou Hospital, Department of General Surgery, Nanjing Medical University, Hangzhou, China.

RESUMEN / SUMMARY: - Ziyuglycoside II is an active compound of Sanguisorba officinalis L. that has anti-inflammation, antioxidation, antibiosis, and homeostasis properties. We report here on the anticancer effect of ziyuglycoside II on human gastric carcinoma BGC-823 cells. We investigated the effects of ziyuglycoside II on cell growth, cell cycle, and cell apoptosis of this cell line. Our results revealed that ziyuglycoside II could inhibit the proliferation of BGC-823 cells by inducing apoptosis but not cell cycle arrest, which was associated with regulation of Bax/Bcl-2 expression, and activation of the caspase-3 pathway. Our study is the first to report the antitumor potential of

ziyuglycoside II in BGC-823 gastric cancer cells. Ziyuglycoside II may become a potential therapeutic agent against gastric cancer in the future.

[820]

TÍTULO / TITLE: - Increased PRAME-Specific CTL Killing of Acute Myeloid Leukemia Cells by Either a Novel Histone Deacetylase Inhibitor Chidamide Alone or Combined Treatment with Decitabine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e70522. doi: 10.1371/journal.pone.0070522. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0070522](#)

AUTORES / AUTHORS: - Yao Y; Zhou J; Wang L; Gao X; Ning Q; Jiang M; Wang J; Wang L; Yu L

INSTITUCIÓN / INSTITUTION: - Department of Hematology and BMT Center, Chinese PLA General Hospital, Beijing, China.

RESUMEN / SUMMARY: - As one of the best known cancer testis antigens, PRAME is overexpressed exclusively in germ line tissues such as the testis as well as in a variety of solid and hematological malignant cells including acute myeloid leukemia. Therefore, PRAME has been recognized as a promising target for both active and adoptive anti-leukemia immunotherapy. However, in most patients with PRAME-expressing acute myeloid leukemia, PRAME antigen-specific CD8(+) CTL response are either undetectable or too weak to exert immune surveillance presumably due to the inadequate PRAME antigen expression and PRAME-specific antigen presentation by leukemia cells. In this study, we observed remarkably increased PRAME mRNA expression in human acute myeloid leukemia cell lines and primary acute myeloid leukemia cells after treatment with a novel subtype-selective histone deacetylase inhibitor chidamide in vitro. PRAME expression was further enhanced in acute myeloid leukemia cell lines after combined treatment with chidamide and DNA demethylating agent decitabine. Pre-treatment of an HLA-A0201(+) acute myeloid leukemia cell line THP-1 with chidamide and/or decitabine increased sensitivity to purified CTLs that recognize PRAME(100-108) or PRAME(300-309) peptide presented by HLA-A0201. Chidamide-induced epigenetic upregulation of CD86 also contributed to increased cytotoxicity of PRAME antigen-specific CTLs. Our data thus provide a new line of evidence that epigenetic upregulation of cancer testis antigens by a subtype-selective HDAC inhibitor or in combination with hypomethylating agent increases CTL cytotoxicity and may represent a new opportunity in future design of treatment strategy targeting specifically PRAME-expressing acute myeloid leukemia.

[821]

TÍTULO / TITLE: - Tumor necrosis factor-related apoptosis-inducing ligand translates neonatal respiratory infection into chronic lung disease.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mucosal Immunol. 2013 Sep 18. doi: 10.1038/mi.2013.65.

●● Enlace al texto completo (gratis o de pago) [1038/mi.2013.65](#)

AUTORES / AUTHORS: - Starkey MR; Essilfie AT; Kim RY; Hatchwell LM; Collison AM; Yagita H; Foster PS; Horvat JC; Mattes J; Hansbro PM

INSTITUCIÓN / INSTITUTION: - Priority Research Centre for Asthma and Respiratory Disease, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle and Hunter Medical Research Institute, New Lambton Heights, Newcastle, New South Wales, Australia.

RESUMEN / SUMMARY: - Respiratory infections in early life can lead to chronic respiratory disease. Chlamydia infections are common causes of respiratory disease, particularly pneumonia in neonates, and are linked to permanent reductions in pulmonary function and the induction of asthma. However, the immune responses that protect against early-life infection and the mechanisms that lead to chronic lung disease are incompletely understood. Here we identify novel roles for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in promoting Chlamydia respiratory infection-induced pathology in early life, and subsequent chronic lung disease. By infecting TRAIL-deficient neonatal mice and using neutralizing antibodies against this factor and its receptors in wild-type mice, we demonstrate that TRAIL is critical in promoting infection-induced histopathology, inflammation, and mucus hypersecretion, as well as subsequent alveolar enlargement and impaired lung function. This suggests that therapeutic agents that target TRAIL or its receptors may be effective treatments for early-life respiratory infections and associated chronic lung disease. Mucosal Immunology advance online publication, 18 September 2013; doi:10.1038/mi.2013.65.

[822]

TÍTULO / TITLE: - Cadmium modifies the cell cycle and apoptotic profiles of human breast cancer cells treated with 5-Fluorouracil.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Aug 12;14(8):16600-16. doi: 10.3390/ijms140816600.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140816600](#)

AUTORES / AUTHORS: - Asara Y; Marchal JA; Carrasco E; Boulaiz H; Solinas G; Bandiera P; Garcia MA; Farace C; Montella A; Madeddu R

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, University of Sassari, Viale San Pietro 43/B, Sassari 07100, Italy. jmarchal@ugr.es.

RESUMEN / SUMMARY: - Industrialisation, the proximity of factories to cities, and human work activities have led to a disproportionate use of substances containing heavy metals, such as cadmium (Cd), which may have deleterious effects on human health.

Carcinogenic effects of Cd and its relationship with breast cancer, among other tumours, have been reported. 5-Fluorouracil (5-FU) is a fluoropyrimidine anticancer drug used to treat solid tumours of the colon, breast, stomach, liver, and pancreas. The purpose of this work was to study the effects of Cd on cell cycle, apoptosis, and gene and protein expression in MCF-7 breast cancer cells treated with 5-FU. Cd altered the cell cycle profile, and its effects were greater when used either alone or in combination with 5-FU compared with 5-FU alone. Cd significantly suppressed apoptosis of MCF-7 cells pre-treated with 5-FU. Regarding gene and protein expression, bcl2 expression was mainly upregulated by all treatments involving Cd. The expression of caspase 8 and caspase 9 was decreased by most of the treatments and at all times evaluated. C-myc expression was increased by all treatments involving Cd, especially 5-FU plus Cd at the half time of treatment. Cd plus 5-FU decreased cyclin D1 and increased cyclin A1 expression. In conclusion, our results indicate that exposure to Cd blocks the anticancer effects of 5-FU in MCF-7 cells. These results could have important clinical implications in patients treated with 5-FU-based therapies and who are exposed to high levels of Cd.

[823]

TÍTULO / TITLE: - The Prognostic Significance of CD44V6, CDH11, and beta-Catenin Expression in Patients with Osteosarcoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:496193. doi: 10.1155/2013/496193. Epub 2013 Jul 18.

●● Enlace al texto completo (gratis o de pago) [1155/2013/496193](#)

AUTORES / AUTHORS: - Deng Z; Niu G; Cai L; Wei R; Zhao X

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Zhongnan Hospital of Wuhan University, No. 169 Donghu Road, Wuhan, Hubei Province 430071, China.

RESUMEN / SUMMARY: - This study aimed to examine the expression of and the relationship between CD44V6, CDH11, and beta-catenin. The expression of these cell adhesion molecules was detected in 90 osteosarcoma and 20 osteochondroma specimens using immunohistochemistry. Associations between these parameters and clinicopathological data were also examined. The expression rates of CD44V6, CDH11, and beta-catenin were 25.0% (5/20), 70.0% (14/20), and 20.0% (4/20) in osteochondroma specimens, respectively. Compared to osteochondromas, the proportions of expression of CD44V6 and beta-catenin in osteosarcoma specimens increased to 65.6% (59/90) and 60.0% (54/90), respectively. However, the expression rate of CDH11 in osteosarcomas was reduced to 40.0% (36/90). The expression of these markers was significantly associated with metastasis and overall survival ($P < 0.05$). Survival analysis revealed that patients with increased expression of CD44V6 and beta-catenin as well as decreased expression of CDH11 were correlated with a shorter survival time. Multivariate analysis indicated that clinical stage, metastasis status, and

the expression of CD44V6, CDH11, and beta -catenin were found to be associated with overall survival. Further, the expression of beta -catenin and that of CD44V6 were positively correlated with each other. Thus, our results indicated abnormal expression of CD44V6, CDH11, and beta -catenin in osteosarcomas and osteochondromas, which may provide important indicators for further research.

Biomed Res Int -----
----- [824]

TÍTULO / TITLE: - Decreased 5-hydroxymethylcytosine (5-hmC) is an independent poor prognostic factor in gastric cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biomed Nanotechnol. 2013 Sep;9(9):1607-16.

AUTORES / AUTHORS: - Yang Q; Wu K; Ji M; Jin W; He N; Shi B; Hou P

INSTITUCIÓN / INSTITUTION: - Department of Endocrinology, The First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Xi'an 710061, The People's Republic of China.

RESUMEN / SUMMARY: - DNA methylation at the 5 position of cytosine (5-mC) is a key epigenetic mark that is involved in various biological and pathological processes. 5-mC can be converted to 5-hydroxymethylcytosine (5-hmC) by the ten-eleven translocation (TET) family of DNA hydroxylases. Increasing evidence suggests that large-scale loss of 5-hmC is an epigenetic hallmark of several human cancers. However, the value of 5-hmC in diagnosis and prognosis of human cancers, including gastric cancer (GC), remains largely unknown. The aim of this study is to determine 5-hmC levels in GCs and explore its association with clinicopathological characteristics and clinical outcome of GC patients. Using immunohistochemistry (IHC) and dot-blot assays, we demonstrated that 5-hmC was dramatically decreased in GCs compared with matched normal tissues. We also found a strong link between decreased 5-hmC and the reduction of TET1 gene expression, but not TET2 or 3, suggesting that decreased TET1 expression might be one of the mechanisms underlying 5-hmC loss in GCs. Wilcoxon tests showed that 5-hmC content was significantly associated with most of clinicopathological characteristics, such as tumor size ($P = 0.016$), Bormman type ($P < 0.0001$), tumor invasion ($P = 0.001$), TNM stage ($P < 0.0001$), the number of lymph nodes metastasis ($P = 0.002$), and survival status ($P < 0.0001$). It is noteworthy that decreased 5-hmC was significantly associated with poor survival of GC patients. Collectively, our findings indicate that decreased 5-hmC may be crucial to the clinical pathology of GC and is a strong and independent poor prognostic factor in GCs.

[825]

TÍTULO / TITLE: - Expression of CD44v6 and integrin-ss1 for the prognosis evaluation of pancreatic cancer patients after cryosurgery.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Diagn Pathol. 2013 Sep 2;8(1):146.

●● Enlace al texto completo (gratuito o de pago) [1186/1746-1596-8-146](https://doi.org/10.1186/1746-1596-8-146)

AUTORES / AUTHORS: - Chiu D; Zhou G; Qin D; Niu L; Cai J; He L; Tan D; Kecheng X

RESUMEN / SUMMARY: - BACKGROUND: Many previous studies demonstrated that cell adhesion molecules CD44v6 and integrin-ss1 had been extensively investigated as potential prognostic markers of various cancers. However, data in PC are scarce. METHODS: We now investigate CD44v6 and integrin-ss1 mRNA expression in PBMC by a triplex real-time RT-PCR assay and protein expression in plasma by ELISA. All specimens were collected from 54 PC patients who received the treatment of cryosurgery as well as 20 healthy individuals (control). RESULTS: The mRNA and protein expression levels of CD44v6 and integrin-ss1 in patients were significantly increased compared with control group ($P < 0.05$). The high CD44v6 mRNA and protein expression were significantly correlated with clinical stage, tumor differentiation, LNM, liver metastasis and decreased median DFS ($P < 0.05$), while the high integrin-ss1 mRNA and protein expression were significantly correlated with clinical stage, LNM, liver metastasis and decreased median DFS ($P < 0.05$). Clinical stage, LNM, liver metastasis, CD44v6 mRNA and protein expression were the independent predictors of survival in PC patients ($P < 0.05$). Moreover, CD44v6 and integrin-ss1 mRNA and protein expression levels were significantly decreased in patients in 3 months after cryosurgery ($P < 0.05$). No significant difference was found in CD44v6 mRNA and protein expression between patients in 3 months after cryosurgery and control group ($P > 0.05$). CONCLUSION: CD44v6 and integrin-ss1 mRNA and protein expression in blood may serve as biomarkers for the development and metastasis of PC, and as prognostic indicators for PC. They may become useful predictors in assessing outcome of PC patients after cryosurgery. Virtual slides The virtual slides for this article can be found here: diagnosticpathology.diagnomx.eu/vs/4035308681009006.

[826]

TÍTULO / TITLE: - Prevalence of known prognostic factors in female breast carcinoma including oestrogen receptor, progesterone receptor and Her-2/neu status—a study in a tertiary care centre.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Indian Med Assoc. 2012 Dec;110(12):876-9.

AUTORES / AUTHORS: - Chakrabarti S; Karmakar R; Barui G; Maity PK; Bandyopadhyay A; Roy A

INSTITUCIÓN / INSTITUTION: - Department of Pathology, RG Kar Medical College, Kolkata 700004.

RESUMEN / SUMMARY: - Breast cancer is second most common cancer in Indian women. It is often curable by various treatment modalities when detected in early stage. Prognosis and selection of therapy in breast cancer depends upon various factors including clinical parameters, histopathological subtype and molecular characteristics of primary tumour. The aim of this study was to determine the prevalence of different

prognostics factors including immunohistochemical marker ie, oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (Her-2/neu) status in female breast carcinoma in a tertiary care centre. In this study 80 females patients who were found to have carcinoma of breast by fine needle aspiration cytology (FNAC) and consequently confirmed by histopathology were followed up for one year. Immunohistochemical staining for molecular markers like oestrogen receptor (ER), progesterone receptor (PR) and Her-2/neu were done in selected 48 cases. Various clinical parameters, cytopathological and hispathological findings as well as immunohistochemical studies were correlated to know the prevalence of these important prognostic factors. It was found that majority of patients were under 50 years of age group with high parity status. Significant patients had breast lump > 4 cm in size. Infiltrating duct carcinoma not otherwise specified (NOS) was the most common histological type showing predominantly microscopic grade II as per Nottingham's Modification of Bloom Richardson grading system. Immunohistochemistry showed 75% ER positivity, 66.66% PR positivity and 25% Her-2/neu positivity.

[827]

TÍTULO / TITLE: - Prognostic value of radiological response to chemotherapy in patients with osteosarcoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e70015. doi: 10.1371/journal.pone.0070015. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0070015

AUTORES / AUTHORS: - Miwa S; Takeuchi A; Shirai T; Taki J; Yamamoto N; Nishida H; Hayashi K; Tanzawa Y; Kimura H; Igarashi K; Ooi A; Tsuchiya H

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, Kanazawa University School of Medicine, Kanazawa, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Chemotherapy is essential to improve the prognosis of the patients with osteosarcoma, and the response to chemotherapy is an important prognostic factor. In this study, the impact of various radiological examinations on overall survival (OS) and event-free survival (EFS) was evaluated. METHOD: Eighty-two patients with high-grade osteosarcoma were included in this study, and we evaluated the following factors for prognostic significance: age (>/=40 years), gender (male), tumor location (truncal site), metastatic disease, histological response to chemotherapy, radiological response to chemotherapy assessed using X-ray, angiography, CT, MRI, (201)Tl scintigraphy, and (99m)Tc-MIBI scintigraphy ((99m)Tc-MIBI), and combined radiological score (CRS). RESULTS: Univariate analyses revealed that metastatic disease, histological response, (99m)Tc-MIBI, and CRS were significantly correlated with OS. Multivariate analyses showed that metastatic disease

(OS: HR 35.9, $P < 0.001$; EFS: HR 17.32, $P < 0.001$) was an independent predictor of OS and EFS. Tumor location (HR 36.1, $P = 0.003$), histological response (HR 31.1, $P = 0.036$), and (99m)Tc-MIBI (HR 18.4, $P = 0.038$) were significant prognostic factors for OS. Moreover, CRS was a marginally significant predictor of OS and EFS. CONCLUSION: The chemotherapeutic effects evaluated by (99m)Tc-MIBI and CRS could be considered as prognostic factors in osteosarcoma.

[828]

TÍTULO / TITLE: - Prognostic value of histological response to chemotherapy in osteosarcoma patients receiving tumor-bearing frozen autograft.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 15;8(8):e71362. doi: 10.1371/journal.pone.0071362.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071362](https://doi.org/10.1371/journal.pone.0071362)

AUTORES / AUTHORS: - Miwa S; Takeuchi A; Ikeda H; Shirai T; Yamamoto N; Nishida H; Hayashi K; Tanzawa Y; Kimura H; Igarashi K; Tsuchiya H

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, Kanazawa University School of Medicine, Kanazawa, Japan.

RESUMEN / SUMMARY: - BACKGROUND: A variety of surgical procedures are now available for tissue reconstruction after osteosarcoma excision, and an important prognostic factor is the evaluation of response to chemotherapy using histology. Although tumor-bearing autografts are useful tools for reconstruction, re-use of the primary tumor may make it difficult to assess the histological response to chemotherapy, since the entire tumor cannot be analyzed. Here, we analyzed the prognostic value of the histological response in the patients who received frozen tumor-bearing autografts for reconstruction. METHOD: Retrospective analysis of the medical records of 51 patients with high-grade osteosarcoma of the extremities was performed. All patients received reconstruction using frozen tumor-bearing autografts. Tumor necrosis was evaluated in extraskeletal masses and cancellous bone. RESULTS: Five-year overall survival of patients with good and poor response to chemotherapy was 82.9% and 46.4%, respectively ($P = 0.044$), and 5-year event-free survival was 57.7% and 36.0%, respectively ($P = 0.329$). Multivariate analysis revealed that a poor histological response to chemotherapy was a significant prognostic factor for overall survival ($P = 0.033$). CONCLUSION: Histological response is an important and reliable prognostic factor in patients undergoing reconstruction using frozen tumor-bearing autografts.

[829]

TÍTULO / TITLE: - Targeted therapy in prostate cancer: is there hope beyond the androgen receptor?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncology (Williston Park). 2013 Jul;27(7):628, 630, 637-8.

AUTORES / AUTHORS: - Alumkal JJ; Graff JN; Beer TM

INSTITUCIÓN / INSTITUTION: - Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, USA.

[830]

TÍTULO / TITLE: - Correction to Induction of Apoptosis by the Anthocyanidins through Regulation of Bcl-2 Gene and Activation of c-Jun N-Terminal Kinase Cascade in Hepatoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Agric Food Chem. 2013 Aug 28;61(34):8241. doi: 10.1021/jf403506x. Epub 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1021/jf403506x](#)

AUTORES / AUTHORS: - Yeh CT; Yen GC

[831]

TÍTULO / TITLE: - Up regulation of serum tumor necrosis factor-related apoptosis inducing ligand in juvenile-onset systemic lupus erythematosus: relations with disease activity, antibodies to double-stranded DNA, nephritis and neutropenia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Rheum Dis. 2013 Jun;16(3):310-8. doi: 10.1111/1756-185X.12061. Epub 2013 Apr 27.

●● Enlace al texto completo (gratis o de pago) [1111/1756-185X.12061](#)

AUTORES / AUTHORS: - Ezzat MH; El-Gammasy TM; Shaheen KY; El-Mezdawi RA; Youssef MS

INSTITUCIÓN / INSTITUTION: - Pediatric Rheumatology Unit, Children's Hospital, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

RESUMEN / SUMMARY: - **OBJECTIVES:** Apoptosis is induced by binding of death receptor ligands, members of the tumor necrosis factor (TNF) superfamily, to their cognate receptors. It is suggested that TNF-related apoptosis inducing ligand (TRAIL) is involved in pathogenesis of juvenile-onset systemic lupus erythematosus (JSLE). This study aimed to assess TRAIL concentrations in sera of JSLE children and to determine their potential relationship with disease activity, anti-double-stranded DNA (anti-dsDNA) levels, neutropenia and renal involvement. **METHODS:** Circulating levels of TRAIL were measured by enzyme-linked immunosorbent assay (ELISA) in serum samples obtained from 40 JSLE patients (20 with active and 20 with inactive disease) and 20 controls. **RESULTS:** The mean (SEM) serum TRAIL concentration in JSLE was 1750.7 (440.2) pg/mL. Serum TRAIL concentrations in patients were higher than those in controls ($P < 0.01$). Serum TRAIL concentrations for children with inactive disease (1854.8 [485.4] pg/mL) and those with activity (1646.6 [390.6] pg/mL) were statistically comparable.

JSLE children with positive anti-dsDNA antibodies had significantly higher TRAIL levels (mean = 1846 [456] vs. 1455 [325] pg/mL; $P < 0.05$). Serum TRAIL concentrations were significantly higher in classes III and IV nephritis compared to classes I and II nephritis (1970 [512] vs. 1330 [331] pg/mL; $P < 0.01$). Serum TRAIL concentrations in patients with neutropenia were higher than those without neutropenia (1805 [505] vs. 1516 [400] pg/mL; $P = 0.042$) and in controls ($P = 0.024$). CONCLUSIONS: Our data indicate that an increased level of TRAIL is a feature of JSLE that correlates with disease activity, anti-dsDNA titers neutropenia and lupus nephritis.

[832]

TÍTULO / TITLE: - Karyotypically abnormal human ESCs are sensitive to HDAC inhibitors and show altered regulation of genes linked to cancers and neurological diseases.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Stem Cell Res. 2013 Jul 18;11(3):1022-1036. doi: 10.1016/j.scr.2013.07.002.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.scr.2013.07.002](#)

AUTORES / AUTHORS: - Lund RJ; Emani MR; Barbaric I; Kivinen V; Jones M; Baker D; Gokhale P; Nykter M; Lahesmaa R; Andrews PW

INSTITUCIÓN / INSTITUTION: - Centre for Stem Cell Biology, Department of Biomedical Science, The University of Sheffield, Sheffield S10 2TN, UK; Turku Centre for Biotechnology, University of Turku and Abo Akademi University, Turku FI-20520, Finland. Electronic address: riikka.lund@btk.fi.

RESUMEN / SUMMARY: - Genomic abnormalities may accumulate in human embryonic stem cells (hESCs) during in vitro maintenance. Characterization of the mechanisms enabling survival and expansion of abnormal hESCs is important due to consequences of genetic changes for the therapeutic utilization of stem cells. Furthermore, these cells provide an excellent model to study transformation in vitro. We report here that the histone deacetylase proteins, HDAC1 and HDAC2, are increased in karyotypically abnormal hESCs when compared to their normal counterparts. Importantly, similar to many cancer cell lines, we found that HDAC inhibitors repress proliferation of the karyotypically abnormal hESCs, whereas normal cells are more resistant to the treatment. The decreased proliferation correlates with downregulation of HDAC1 and HDAC2 proteins, induction of the proliferation inhibitor, cyclin-dependent kinase inhibitor 1^a (CDKN1A), and altered regulation of tumor suppressor protein Retinoblastoma 1 (RB1). Through genome-wide transcriptome analysis we have identified genes with altered expression and responsiveness to HDAC inhibition in abnormal cells. Most of these genes are linked to severe developmental and neurological diseases and cancers. Our results highlight the importance of epigenetic mechanisms in the regulation of genomic stability of hESCs, and provide valuable candidates for targeted and selective growth inhibition of karyotypically abnormal cells.

[833]

TÍTULO / TITLE: - An Analysis of the Prognostic Value of IDH1 (Isocitrate Dehydrogenase 1) Mutation in Polish Glioma Patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Diagn Ther. 2013 Aug 10.

●● Enlace al texto completo (gratis o de pago) [1007/s40291-013-0050-7](#)

AUTORES / AUTHORS: - Lewandowska MA; Furtak J; Szyberg T; Roszkowski K; Windorbska W; Rytlevska J; Jozwicki W

INSTITUCIÓN / INSTITUTION: - Molecular Oncology and Genetics Unit, Department of Tumor Pathology and Pathomorphology, The Franciszek Lukaszczuk Oncology Center, dr I. Romanowskiej 2, 85-796, Bydgoszcz, Poland, lewandowskam@co.bydgoszcz.pl.

RESUMEN / SUMMARY: - BACKGROUND AND OBJECTIVE: IDH1 (isocitrate dehydrogenase 1) is a potential biomarker and drug target. Genomic and epigenetic data on astrocytoma have demonstrated that the IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Furthermore, recent studies have also indicated that a mutant IDH1 inhibitor induced demethylation of histone H3K9me3 and expression of genes associated with gliogenic differentiation. As the presence of the p.R132H mutation in the IDH1 gene seems to be a more powerful prognostic marker than O6-methylguanine-DNA methyltransferase promoter status, we evaluated the presence of IDH1 mutation in Polish patients with astrocytoma, glioblastoma, oligoastrocytoma, ganglioglioma, oligodendroglioma, and ependymoma. METHODS: The IDH1 mutation status at codon 132 was determined using a mouse monoclonal antibody specific for the R132H mutation, direct sequencing, and Co-amplification at Lower Denaturation Temperature (COLD) polymerase chain reaction (PCR) high-resolution melting-curve analysis (HRM). RESULTS: Wild-type (WT) IDH1 was detected in cases with a World Health Organization (WHO) grade I astrocytoma. The IDH1 c.G395A; p.R132H mutation was observed in 56 and 94 % of grade II and grade III astrocytoma cases, respectively. Significant differences in the median overall survival were observed in astrocytoma patients grouped on the basis of the presence of IDH1 mutation: survival was 24 months longer in grade II astrocytoma and 12 months longer in glioblastoma. Overall survival was compared between grade II astrocytoma patients with low or high expression of the mutant protein. Interestingly, lower R132H expression correlated with better overall survival. CONCLUSION: Our results indicate the usefulness of assessing the R132H IDH1 mutation in glioma patients: the presence or absence of the R132H mutation can help pathologists to distinguish pilocytic astrocytomas (IDH1 WT) from diffuse ones (R132H IDH1/WT). Moreover, low IDH1 p.R132H expression was related to better prognosis. This clinical implication appears to be important for personalization of prognosis and treatment by oncologists.

[834]

TÍTULO / TITLE: - Steroid sulfatase inhibitors: promising new therapy for breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Pak Med Assoc. 2013 Apr;63(4):509-15.

AUTORES / AUTHORS: - Sadozai H

INSTITUCIÓN / INSTITUTION: - MBS Biomedical Sciences, University of Guelph, Guelph, Ontario. hsadozai@uoguelph.ca

RESUMEN / SUMMARY: - Manipulation of the hormone oestrogen has been used for decades to treat hormone-dependent breast cancer. Currently, aromatase inhibitors (AIs) are used as first-line therapy against early and metastatic breast cancer in post-menopausal women. Despite these advances, several patients eventually experience a relapse of breast cancer and declined clinical response to treatment. As per recent findings, steroid sulfatase (STS) has emerged as a novel therapy target. This review aims at summarising the emerging field of STS inhibitor development and highlighting current findings from pre-clinical and clinical trials. The recently-developed dual-targeting compounds, such as dual aromatase-sulfatase inhibitors (DASI), have shown encouraging preclinical results and represent important new treatments for hormone-dependent breast cancer.

[835]

TÍTULO / TITLE: - Clinical analysis and prognostic significance of hepatitis B virus infections for diffuse large B-cell lymphoma with or without rituximab therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Exp Ther Med. 2013 Jul;6(1):109-114. Epub 2013 Apr 25.

●● [Enlace al texto completo \(gratis o de pago\) 3892/etm.2013.1079](#)

AUTORES / AUTHORS: - Xie W; Zhou D; Hu K; Xiao X; Huang W; He J; Shi J; Luo Y; Zhang J; Lin M; Cai Z; Huang H; Ye X

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Bone Marrow Transplant Center, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003;

RESUMEN / SUMMARY: - The aim of this study was to analyze the clinical features of hepatitis B surface antigen (HBsAg)-positive and negative diffuse large B-cell lymphomas (DLBCLs) and to compare the outcomes and serum hepatitis B virus (HBV)-DNA loads of patients treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimens with rituximab (RCHOP) or without. A total of 451 DLBCL patients, of which 90 were HBsAg-positive and 361 were HBsAg-negative, were retrospectively reviewed. We compared onset age, gender, Ann Arbor stage, international prognostic index (IPI), lactate dehydrogenase (LDH) and beta2-microglobulin (beta2-M) levels, as well as overall survival (OS) rates and HBV-DNA loads under CHOP or RCHOP regimens. The OS rate of the HBsAg-positive DLBCL patients was significantly lower than that of HBsAg-negative DLBCL patients and the

HBsAg-positive DLBCL patients had an earlier median onset age. HBsAg-positive DLBCL patients had poorer OS rates compared with HBsAg-negative patients (62.2% HBsAg-positive vs. 76.2% HBsAg-negative, $P=0.018$). HBsAg-positive DLBCL patients with HBV-DNA loads >103 cps/ml during chemotherapy had significantly lower OS rates than those with lower HBV-DNA loads (48.4% HBV-DNA elevated vs. 71.2% HBV-DNA normal, $P=0.037$). HBsAg-positive DLBCL patients treated with RCHOP had a significantly higher OS rate (79.6%) compared with the 41 CHOP-treated patients (43.9%; $P<0.001$). HBsAg-positive DLBCL patients with an earlier median onset age and elevated HBV-DNA during chemotherapy had poorer prognoses. HBsAg and HBV-DNA during chemotherapy may be used as prognostic indicators for patients with DLBCL. Rituximab improves the outcome of HBsAg-positive DLBCL patients when administered in combination with anti-viral lamivudine.

[836]

TÍTULO / TITLE: - The value of serum albumin as a novel independent marker for prognosis in patients with endometrial cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Obstet Gynecol Reprod Biol. 2013 Aug 11. pii: S0301-2115(13)00373-4. doi: 10.1016/j.ejogrb.2013.07.044.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejogrb.2013.07.044

AUTORES / AUTHORS: - Seebacher V; Grimm C; Reinthaller A; Heinze G; Tempfer C; Hefler L; Polterauer S

INSTITUCIÓN / INSTITUTION: - Department of Gynecology and Gynecological Oncology, Comprehensive Cancer Center Vienna, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. Electronic address:

veronika.seebacher@meduniwien.ac.at.

RESUMEN / SUMMARY: - OBJECTIVE: Hypoalbuminemia, a known marker for malnutrition and increased morbidity and mortality, has been associated with impaired prognosis in different cancer entities. The present study investigates the prognostic value of pre-treatment serum albumin levels for survival in patients with endometrial cancer.

STUDY DESIGN: Within the present cohort study, we evaluated 337 consecutive patients with endometrial cancer and investigated the association of pre-treatment serum albumin levels and clinical-pathological parameters. We performed univariate log-rank tests and multivariable Cox regression models to assess the association between pre-treatment serum albumin levels and survival. RESULTS: Pre-treatment serum albumin levels were inversely proportionally associated with FIGO tumor stage, histological grade, and patients' age. In a multivariable analysis pre-treatment serum albumin levels ($p=0.02$ and $p=0.001$), FIGO tumor stage ($p<0.001$ and $p<0.001$), and histological grade ($p=0.002$ and $p<0.001$) were independently associated with disease-free and progression-free survival, respectively. CONCLUSION: Pre-treatment serum

albumin is a novel and independent prognostic parameter for disease-free and progression-free survival in patients with endometrial cancer.

[837]

TÍTULO / TITLE: - Molecular Mechanism Underlying Hesperetin-induced Apoptosis by in silico Analysis and in Prostate Cancer PC-3 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(7):4347-52.

AUTORES / AUTHORS: - Sambantham S; Radha M; Paramasivam A; Anandan B; Malathi R; Chandra SR; Jayaraman G

INSTITUCIÓN / INSTITUTION: - Department of Genetics, University of Madras, Chennai, India E-mail : nchandrarsamuel@gmail.com.

RESUMEN / SUMMARY: - Aim: To investigate the molecular mechanisms underlying triggering of apoptosis by hesperetin using in silico and in vitro methods. Methods: The mechanism of binding of hesperetin with NF- κ B and other apoptotic proteins like BAX, BAD, BCL2 and BCLXL was analysed in silico using Schrodinger suite 2009. In vitro studies were also carried out to evaluate the potency of hesperetin in inducing apoptosis using the human prostate cancer PC-3 cell line. Results: Hesperetin was found to exhibit high-affinity binding resulting from greater intermolecular forces between the ligand and its receptor NF- κ B (-7.48 Glide score). In vitro analysis using MTT assay confirmed that hesperetin reduced cell proliferation (IC50 values of 90 and 40 μ M at 24 and 48h respectively) in PC-3 cells. Hesperetin also downregulated expression of the anti-apoptotic gene BCLXL at both mRNA and protein levels and increased the expression of pro-apoptotic genes like BAD at mRNA level and BAX at mRNA as well as protein levels. Conclusion: The results suggest that hesperetin can induce apoptosis by inhibiting NF- κ B.

[838]

TÍTULO / TITLE: - Effects of polymorphisms in translesion DNA synthesis genes on lung cancer risk and prognosis in Chinese men.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Epidemiol. 2013 Sep 5. pii: S1877-7821(13)00118-5. doi: 10.1016/j.canep.2013.08.003.

●● Enlace al texto completo (gratis o de pago) 1016/j.canep.2013.08.003

AUTORES / AUTHORS: - Xu HL; Gao XR; Zhang W; Cheng JR; Tan YT; Zheng W; Shu XO; Xiang YB

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200032, China; State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer

Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200032, China.

RESUMEN / SUMMARY: - PURPOSE: Translesion DNA synthesis (TLS) plays an important role in promoting replication through DNA lesions. Genetic polymorphisms in TLS genes may have potential roles in lung cancer development in humans. METHODS: We evaluated the association between genetic variants in six TLS genes and the risk and survival of lung cancer in a case-control study in China. Included in the study are 224 lung cancer patients and 448 healthy controls. RESULTS: Carriers of the G allele of POLKappa rs5744724 had significantly reduced risk of lung cancer (odds ratio (OR)=0.62, 95% confidence interval (CI): 0.44-0.89), comparing with those carrying the C allele, and the AA genotype of PCNA rs25406 was also associated with significantly decreased cancer risk compared with the major homozygote alleles (OR=0.47, 95% CI: 0.25-0.86). Haplotype analysis showed that subjects with the POLKappa C-G (rs5744533-rs5744724) haplotype had decreased risk of lung cancer (OR=0.69, 95% CI: 0.49-0.98), comparing with those carrying the C-C haplotype. Besides, the heterozygote of REV1 rs3087386 and rs3792136 were independent prognostic factors for lung cancer survival with hazard ratio (HR) 1.54 (95% CI: 1.12-2.12) and 1.44 (95% CI: 1.06-1.97) respectively. CONCLUSIONS: Our findings suggested that genetic variants in POLKappa and PCNA genes may play roles in the susceptibility of lung cancer, and REV1 gene may have roles in lung cancer survival in Chinese men.

[839]

TÍTULO / TITLE: - EMMPRIN Promotes Angiogenesis, Proliferation, Invasion and Resistance to Sunitinib in Renal Cell Carcinoma, and Its Level Predicts Patient Outcome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 20;8(9):e74313. doi: 10.1371/journal.pone.0074313.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074313](https://doi.org/10.1371/journal.pone.0074313)

AUTORES / AUTHORS: - Sato M; Nakai Y; Nakata W; Yoshida T; Hatano K; Kawashima A; Fujita K; Uemura M; Takayama H; Nonomura N

INSTITUCIÓN / INSTITUTION: - The Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan.

RESUMEN / SUMMARY: - PURPOSE: Extracellular matrix metalloproteinase inducer (EMMPRIN) has been reported to play crucial roles, including in angiogenesis, in several carcinomas. However, the correlation between EMMPRIN levels and angiogenesis expression profile has not been reported, and the role of EMMPRIN in renal cell carcinoma (RCC) is unclear. In the present study, we evaluated the association of EMMPRIN with angiogenesis, its value in prognosis, and its roles in RCC. EXPERIMENTAL DESIGN: EMMPRIN expression was examined in 50 RCC patients treated with radical nephrectomy. Angiogenesis, proliferation, and invasion activity were evaluated using EMMPRIN knockdown RCC cell lines. The size of EMMPRIN-

overexpressing xenografts was measured and the degree of angiogenesis was quantified. EMMPRIN expression was evaluated in RCC patients who received sunitinib therapy and in sunitinib-resistant cells. Further, the relation between EMMPRIN expression and sensitivity to sunitinib was examined. RESULTS: EMMPRIN score was significantly associated with clinicopathological parameters in RCC patients, as well as being significantly correlated with microvessel area (MVA) in immature vessels and with prognosis. Down-regulation of EMMPRIN by siRNA led to decreased VEGF and bFGF expression, cell proliferation, and invasive potential. EMMPRIN over-expressing xenografts showed accelerated growth and MVA of immature vessels. EMMPRIN expression was significantly increased in patients who received sunitinib therapy as well as in sunitinib-resistant 786-O cells (786-suni). EMMPRIN-overexpressing RCC cells were resistant to sunitinib. CONCLUSION: Our findings indicate that high expression of EMMPRIN in RCC plays important roles in tumor progression and sunitinib resistance. Therefore, EMMPRIN could be a novel target for the treatment of RCC.

[840]

TÍTULO / TITLE: - Prognostic impact and the relevance of PTEN copy number alterations in patients with advanced colorectal cancer (CRC) receiving bevacizumab.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Med. 2013 Jun;2(3):277-85. doi: 10.1002/cam4.75. Epub 2013 Mar 25.

●● [Enlace al texto completo \(gratis o de pago\) 1002/cam4.75](#)

AUTORES / AUTHORS: - Price TJ; Hardingham JE; Lee CK; Townsend AR; Wrin JW; Wilson K; Simes RJ; Murone C; Tebbutt NC

INSTITUCIÓN / INSTITUTION: - Haematology-Oncology Department, The Queen Elizabeth Hospital Woodville, SA, 5011, Australia. timothy.price@health.sa.gov.au

RESUMEN / SUMMARY: - Loss of phosphatase and tensin homologue (PTEN) expression may be prognostic in colorectal cancer (CRC) and may have a correlation with vascular endothelial growth factor (VEGF) expression via hypoxia-inducible factor 1 (HIF-1) alpha, and the PI3K/mTOR pathways. We therefore have explored the prognostic association of PTEN loss and the potential that PTEN loss may be predictive of outcome with bevacizumab. Patients enrolled in the AGITG MAX trial, a randomized Phase III trial of capecitabine © +/- bevacizumab (B) (+/- mitomycin C [M]) with available tissues were analyzed for PTEN expression (loss vs. no loss) as assessed using a Taqman® copy number assay (CNA). Of the original 471 patients enrolled, tissues from 302 (64.1%) patients were analyzed. PTEN loss was observed in 38.7% of patients. There was no relationship between PTEN loss and KRAS or BRAF mutation. PTEN status was not prognostic for progression-free survival (PFS) or overall survival (OS) in multivariate analyses adjusting for other baseline factors; loss versus no loss PFS hazard ratio (HR) 0.9 (0.7-1.16), OS HR 1.04 (0.79-1.38). PTEN was not prognostic when

assessed by KRAS and BRAF status. By using the comparison of C versus CB+CBM, PTEN status was not significantly predictive of the effectiveness of B for PFS or OS. PTEN status was not prognostic for survival in advanced colorectal cancer, irrespective of KRAS or BRAF status. PTEN status did not significantly predict different benefit with bevacizumab therapy.

[841]

TÍTULO / TITLE: - Forced expression of indoleamine-2,3-dioxygenase in human umbilical cord-derived mesenchymal stem cells abolishes their anti-apoptotic effect on leukemia cell lines in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - In Vitro Cell Dev Biol Anim. 2013 Aug 16.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s11626-013-9667-4](#)

AUTORES / AUTHORS: - Lu X; Tao CL; Chen X; Shao HW; Huang SL

INSTITUCIÓN / INSTITUTION: - School of Life Science and Biopharmacology, Guangdong Provincial Key Laboratory of Biotechnology Candidate Drug Research, Guangdong Pharmaceutical University, Guangzhou Higher Education Mega Center, Guangzhou, 510006, Guangdong, China.

RESUMEN / SUMMARY: - The ability of mesenchymal stem cells (MSCs) to preserve cancer cells potentially constitutes the adverse effect of MSC-based cell therapy in the context of hematologic malignancy. In an effort to reverse this undesirable feature of MSCs, we manipulated human umbilical cord-derived MSCs (UC-MSCs) to express indoleamine-2,3-dioxygenase (IDO), an enzyme that induces immune suppression by inhibiting T cell proliferation and triggering apoptosis in immune cells. Cultures of human UC-MSCs were generated by plastic adherence method. Full-length cDNA of human IDO was cloned into adenovirus shuttle vector. Then, the recombinant virus harboring IDO gene was produced in 293 cells and used to infect UC-MSCs. Expression of IDO protein was detected within infected UC-MSCs, and accumulation of kynurenine was observed in the supernatant. Two human leukemia cell lines, Jurkat and HL-60, were cultured on the monolayer of native or infected UC-MSCs, respectively. It was observed that forced IDO expression abolished the anti-apoptotic effect of UC-MSCs on these leukemia cells and enhanced their proliferation inhibitory effect on activated human lymphocytes as well as leukemia cells. These results suggested that equipping MSCs with IDO could be one of the reasonable strategies to reverse their cancer-supportive effect unfavorable for clinical applications.

[842]

TÍTULO / TITLE: - Increased expression of miR-126 and miR-10^a predict prolonged relapse-free time of primary oestrogen receptor-positive breast cancer following tamoxifen treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug 19. pii: S0959-8049(13)00730-2. doi: 10.1016/j.ejca.2013.07.145.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.07.145](#)

AUTORES / AUTHORS: - Hoppe R; Achinger-Kawecka J; Winter S; Fritz P; Lo WY; Schroth W; Brauch H

INSTITUCIÓN / INSTITUTION: - Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany; University Tuebingen, Tuebingen, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Adjuvant tamoxifen is a valid treatment option for women with oestrogen receptor (ER)-positive breast cancer. However, up to 40% of patients experience distant or local recurrence or die. MicroRNAs have been suggested to be important prognosticators in breast cancer. This study aims to identify microRNAs with the potential to predict tamoxifen response. PATIENTS AND METHODS: We performed a global microRNA screen (1105 human microRNAs) in primary tumours of six matched pairs of postmenopausal, ER-positive breast cancer patients treated with tamoxifen, who were either recurrence free or had developed a recurrence (median follow up: 8.84years; range: 1.28-12.7years). Patients of this discovery set and the 81 patients of the validation set (median follow up: 8.64years; range: 0.21-19.85years) were treated at the Robert Bosch Hospital, Stuttgart, Germany, between 1986 and 2005. RESULTS: Out of the top 20 deregulated microRNAs (12 up-regulated, eight down-regulated) miR-126 (Hazard Ratio (HR)=0.56, 95% confidence interval (CI): 0.38-0.83; Holm-adj. P=0.022) and miR-10^a (HR=0.53, 95% CI: 0.33-0.85; Holm-adj. P=0.031) were identified as significant predictors of tamoxifen outcome by multivariate Cox regression analysis in the independent validation set of 81 postmenopausal, ER-positive patients. Kaplan-Meier survival analyses based on cut-offs determined by receiver operating characteristics curves confirmed that a higher expression of miR-126 and miR-10^a in the patients tumour was associated with longer relapse-free time (log-rank P=0.037, P<0.0001, respectively). CONCLUSIONS: Our data suggest that miR-126 and miR-10^a are independent predictors for tumour relapse in early postmenopausal breast cancer patients treated with adjuvant tamoxifen.

[843]

TÍTULO / TITLE: - Growth and differentiation factor 3 induces expression of genes related to differentiation in a model of cancer stem cells and protects them from retinoic Acid-induced apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e70612. doi: 10.1371/journal.pone.0070612.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070612](#)

AUTORES / AUTHORS: - Tykwinska K; Lauster R; Knaus P; Rosowski M

INSTITUCIÓN / INSTITUTION: - Institute of Medical Biotechnology, Department of Biotechnology, Technische Universitat Berlin, Berlin, Germany ; Berlin-Brandenburg

School for Regenerative Therapies, Charite Campus Virchow Klinikum, Berlin, Germany.

RESUMEN / SUMMARY: - Misexpression of growth factors, particularly those related to stem cell-like phenotype, is often observed in several cancer types. It has been found to influence parameters of disease progression like cell proliferation, differentiation, maintenance of undifferentiated phenotype and modulation of the immune system. GDF3 is a TGF β family member associated with pluripotency and differentiation during embryonic development that has been previously reported to be re-expressed in a number of cancer types. However, its role in tumor development and progression has not been clarified yet. In this study we decipher the role of GDF3 in an in vitro model of cancer stem cells, NCCIT cells. By classical approach to study protein function combined with high-throughput technique for transcriptome analysis and differentiation assays we evaluated GDF3 as a potential therapeutic target. We observed that GDF3 robustly induces a panel of genes related to differentiation, including several potent tumor suppressors, without impacting the proliferative capacity. Moreover, we report for the first time the protective effect of GDF3 against retinoic acid-induced apoptosis in cells with stem cell-like properties. Our study implies that blocking of GDF3 combined with retinoic acid-treatment of solid cancers is a compelling direction for further investigations, which can lead to re-design of cancer differentiation therapies.

[844]

TÍTULO / TITLE: - Effect of blocking Ras signaling pathway with K-Ras siRNA on apoptosis in esophageal squamous carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Tradit Chin Med. 2013 Jun;33(3):361-6.

AUTORES / AUTHORS: - Wang X; Zheng Y; Fan Q; Zhang X

INSTITUCIÓN / INSTITUTION: - Department of Integrated Chinese and Western Medicine, First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To study the effect of RNAi silencing of the K-Ras gene on Ras signal pathway activity in EC9706 esophageal cancer cells. **METHODS:** EC9706 cells were treated in the following six groups: blank group (no transfection), negative control group (transfection no-carrier), transfection group (transfected with pSilencer-siK-ras), taxol chemotherapy group, taxol chemotherapy plus no-carrier group, taxol chemotherapy plus transfection group. Immunocytochemistry, Reverse transcription-polymerase chain reaction and western blotting were used to analyze the expression of MAPK1 (mitogen-activated protein kinases 1) and cyclin D1 in response to siRNA (small interfering RNA) transfection and taxol treatment. **RESULTS:** K-Ras (K-Ras gene) siRNA transfection of EC9706 esophageal squamous carcinoma cells decreased the expression of K-Ras, MAPK1 and cyclin D1 at the mRNA and protein level. Reverse transcription-polymerase chain reaction indicated that the expression

levels of MAPK1 and cyclin D1 mRNAs were significantly lower in the transfection group than in the blank group ($P < 0.05$). Western blotting showed that 72 h after EC9706 cell transfection, the expression levels of MAPK1 and cyclin D1 proteins had decreased in all groups, and the expression levels in the transfection group were significantly inhibited as compared with the blank group. Apoptosis increased significantly in the transfection group or after addition of taxol as compared with the blank group and the no-carrier group. The degree of apoptosis in the taxol plus transfection group was more severe. CONCLUSION: Apoptosis increased significantly in EC9706 esophageal carcinoma cells after siRNA-mediated inhibition of Ras signaling, with the most obvious increase observed in the transfection plus taxol chemotherapy group. Ras knockdown therefore increased cellular sensitivity to the chemotherapeutic agent, taxol. Ras knockdown also down-regulated the expression of the downstream genes, MAPK1 and cyclin D1, thus inhibiting the growth, proliferation and metabolism of esophageal cancer cells.

[845]

TÍTULO / TITLE: - Survival of HER2-Positive Breast Cancer Cells: Receptor Signaling to Apoptotic Control Centers.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genes Cancer. 2013 May;4(5-6):187-95. doi: 10.1177/1947601913488598.

- Enlace al texto completo (gratis o de pago) [1177_1947601913488598](#) [pii]
- Enlace al texto completo (gratis o de pago) [1177/1947601913488598](#)

AUTORES / AUTHORS: - Fink MY; Chipuk JE

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Sciences, Long Island University Post, Brookville, NY, USA.

RESUMEN / SUMMARY: - HER2 is overexpressed in a subset of breast cancers and controls an oncogenic signaling network that inhibits tumor cell death through the specific biochemical regulation of apoptotic pathways. In particular, the mitochondrial pathway for apoptosis is important for death induced by inhibitors of HER2. This review focuses on the connections between this oncogenic signaling network and individual components of the mitochondrial pathway. A comprehensive view of this signaling network is crucial for developing novel drugs in this area and to gain an understanding of how these regulatory interactions are altered in drug-refractory cancers.

[846]

TÍTULO / TITLE: - Flavonoid apigenin modified gene expression associated with inflammation and cancer and induced apoptosis in human pancreatic cancer cells through inhibition of GSK-3 β /NF- κ B signaling cascade.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Nutr Food Res. 2013 Aug 14. doi: 10.1002/mnfr.201300307.

●● Enlace al texto completo (gratis o de pago) [1002/mnfr.201300307](#)

AUTORES / AUTHORS: - Johnson JL; de Mejia EG

INSTITUCIÓN / INSTITUTION: - Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, IL, USA.

RESUMEN / SUMMARY: - SCOPE: The objective was to examine the inhibitory effects of citrus fruit bioactive compounds on BxPC-3 and PANC-1 human pancreatic cancer cells, focusing on the antiproliferative mechanism of action of the flavonoid apigenin related to the glycogen synthase kinase-3beta/nuclear factor kappa B signaling pathway. METHODS AND RESULTS: Flavonoids, limonoids, phenolic acids, and ascorbic acid were tested for cytotoxic effects on BxPC-3 and PANC-1 cells; apigenin was the most potent (IC50 = 23 and 12 muM for 24 and 48 h for BxPC-3 and IC50 = 71 and 41 muM for 24 and 48 h for PANC-1). Apigenin induced pancreatic cell death through inhibition of the glycogen synthase kinase-3beta/nuclear factor kappa B signaling pathway. Apigenin arrested cell cycle at G2 /M phase (36 and 32% at 50 muM for BxPC-3 and PANC-1, respectively) with concomitant decrease in the expression of cyclin B1. Apigenin activated the mitochondrial pathway of apoptosis (44 and 14% at 50 muM for BxPC-3 and PANC-1, respectively) and modified the expression of apoptotic proteins. Apigenin highly upregulated the expression of cytokine genes IL17F (114.2-fold), LTA (33.1-fold), IL17C (23.2-fold), IL17A (11.3-fold), and IFNB1 (8.9-fold) in BxPC-3 cells, which potentially contributed to the anticancer properties. CONCLUSION: Flavonoids have a protective role in pancreatic cancer tumorigenesis.

[847]

TÍTULO / TITLE: - Allicin induces anti-human liver cancer cells through p53 gene modulating apoptosis and autophagy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Agric Food Chem. 2013 Sep 23.

●● Enlace al texto completo (gratis o de pago) [1021/jf403241s](#)

AUTORES / AUTHORS: - Chu YL; Ho CT; Chung JG; Rajasekaran R; Lo YC; Sheen LY

RESUMEN / SUMMARY: - Hepatocellular carcinoma is the most prevalent type of liver cancer globally and ranks first among the cancer-related mortalities in Taiwan. This study aims to understand the modes of cell death mechanism induced by allicin, a major phytochemical of crushed garlic, in human hepatoma cells. Our earlier study indicated allicin induced autophagic cell death in human hepatocellular carcinoma Hep G2 (p53wildtype) cells whereas in the present study allicin induced apoptotic cell death through caspase-dependent and -independent pathways by ROS overproduction in human hepatocellular carcinoma Hep 3B (p53mutation) cells. To gain insight into the cell death mechanism in p53 knocked down Hep G2, we silenced p53 gene using siRNA mediated silencing. Allicin treatment induced apoptotic cell death in

p53 knocked down Hep G2 cells similar to that of Hep 3B cells. These results suggest that allicin induced cell death in human hepatoma cells either through autophagy or apoptosis and might be a potential novel complementary gene therapeutic agent for the treatment of either autophagy or apoptosis resistant cancer cells.

[848]

TÍTULO / TITLE: - Kinesin Spindle Protein (KSP) Inhibitors in Combination with Chemotherapeutic Agents for Cancer Therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ChemMedChem. 2013 Aug 21. doi: 10.1002/cmdc.201300228.

●● Enlace al texto completo (gratis o de pago) [1002/cmdc.201300228](#)

AUTORES / AUTHORS: - Song H; Zhou S; Wang R; Li S

INSTITUCIÓN / INSTITUTION: - School of Pharmacy, Shanghai Jiao Tong University, Shanghai (PR China).

RESUMEN / SUMMARY: - A diverse group of proteins, the activities of which are precisely orchestrated during mitosis, have emerged as targets for cancer therapeutics; these include the Aurora kinases (AKs), Polo-like kinases (PLKs), and the kinesin spindle protein (KSP). KSP is essential for the proper separation of spindle poles during mitosis. Agents that target KSP selectively act on cells undergoing cell division, which means that KSP inhibitors are mitosis-specific drugs, and have demonstrated remarkable activities in vitro. However, a significant obstacle to the success of KSP inhibitors is that these compounds, with tremendous efficacy in vitro, have demonstrated little or even no antitumor activity in vivo. Accumulated data suggest that a combination of KSP inhibitors with various cytostatic drugs will result in a more powerful tumor-killing effect than monotherapy. Combination therapies might predominate and represent the next frontier in the discovery research of KSP inhibitors as potential anticancer drugs. Few published studies have reviewed combination therapy using KSP inhibitors. Herein we provide a comprehensive review of the literature on KSP inhibitor monotherapy and therapeutic combinations. The current state and problems are also discussed.

[849]

TÍTULO / TITLE: - Smac mimetic and demethylating agents synergistically trigger cell death in acute myeloid leukemia cells and overcome apoptosis resistance by inducing necroptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 12;4:e802. doi: 10.1038/cddis.2013.320.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.320](#)

AUTORES / AUTHORS: - Steinhart L; Belz K; Fulda S

INSTITUCIÓN / INSTITUTION: - Institute for Experimental Cancer Research in Pediatrics, Goethe-University, Frankfurt, Germany.

RESUMEN / SUMMARY: - Evasion of apoptosis, for example, by inhibitor of apoptosis (IAP) proteins, contributes to treatment resistance and poor outcome in acute myeloid leukemia (AML). Here we identify a novel synergistic interaction between the small-molecule second mitochondria-derived activator of caspases (Smac) mimetic BV6, which antagonizes X-linked IAP, cellular IAP (cIAP)1 and cIAP2, and the demethylating agents 5-azacytidine or 5-aza-2'-deoxycytidine (DAC) to induce cell death in AML cells, including apoptosis-resistant cells. Calculation of combination index (CI) confirms that this drug combination is highly synergistic (CI 0.02-0.4). In contrast, BV6 and DAC at equimolar concentrations do not cause synergistic toxicity against normal peripheral blood lymphocytes, pointing to some tumor cell selectivity. Molecular studies reveal that BV6 and DAC cooperate to trigger the activation of caspases, mitochondrial perturbations and DNA fragmentation, consistent with apoptotic cell death. However, the broad-range caspase inhibitor N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone (zVAD.fmk) fails to protect against BV6/DAC-induced cell death and even significantly increases the percentage of Annexin-V/propidium iodide double-positive cells. Importantly, BV6/DAC-induced cell death in the presence of zVAD.fmk is significantly reduced by pharmacological inhibition of key components of necroptosis signaling, that is, receptor-interacting protein (RIP) 1 using necrostatin-1 or mixed lineage kinase domain-like protein (MLKL) using necrosulfonamide. This indicates a switch from BV6/DAC-induced cell death from apoptosis to necroptosis upon caspase inhibition. Thus, BV6 cooperates with demethylating agents to induce cell death in AML cells and circumvents apoptosis resistance via a switch to necroptosis as an alternative mode of cell death. The identification of a novel synergism of BV6 and demethylating agents has important implications for the development of new treatment strategies for AML.

[850]

TÍTULO / TITLE: - RelB, together with RelA, sustains cell survival and confers proteasome inhibitor sensitivity of chronic lymphocytic leukemia cells from bone marrow.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Med (Berl). 2013 Sep 17.

●● Enlace al texto completo (gratis o de pago) [1007/s00109-013-1081-6](#)

AUTORES / AUTHORS: - Xu J; Zhou P; Wang W; Sun A; Guo F

INSTITUCIÓN / INSTITUTION: - Central Lab, The First Affiliated Hospital of Soochow University, Shizi Road 188, Suzhou, China, 215006.

RESUMEN / SUMMARY: - Although the biological factors that contribute to the pathogenesis of chronic lymphocytic leukemia (CLL) remain widely unresolved, it has been suggested that dysregulated cell survival and proliferation are fundamental to this process. Constitutive classical nuclear factor kappa-light-chain-enhancer of

activated B cells (NF-kappaB) activation protects CLL B-cells from cell death and plays a critical role in the acquisition of chemoresistance. RelB, representing the alternative NF-kappaB activity, functions specifically in lymphoid organogenesis and B-cell maturation. RelB indeed plays a tumor-supportive role and confers radiation resistance in tumors. However, the involvement of RelB in CLL has not been addressed. Here, we analyzed the NF-kappaB activation in 67 of CLL bone marrow (BM). Both the RelA and RelB activity were detected in CLL B-cells from BM, in spite of inevitable variability. Low RelB activity was linked to a favorable prognosis of CLL. The migration and adhesion abilities of CLL B-cells were not affected by the RelB activity. High RelB activity, together with the RelA activity, maintained basal survival of cells. The induction of RelA and RelB expression in the nucleus was responsible for better survival of CLL B-cells supported by bone marrow stromal cells. In addition, the presence of high RelB activity in CLL B-cells was correlated with sensitivity to proteasome inhibitor but not fludarabine. Taken together, we provided evidences that not only RelA but also RelB, subunits of NF-kappaB family, played an important role in the cellular behaviors of CLL cells from BM. The strength of RelB activity influenced the prognosis of CLL patients. KEY MESSAGE: RelB, with RelA activity, maintained the basal survival of CLL cells from BM. RelB, with RelA, conferred the proteasome inhibitor sensitivity of CLL cells. Induction of RelA and RelB was responsible for the better survival of CLL B-cells. The strength of RelB activity influenced the prognosis of CLL patients.

[851]

TÍTULO / TITLE: - P-glycoprotein expression as a predictor of response to neoadjuvant chemotherapy in breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Indian J Cancer. 2013 Jul-Sep;50(3):195-9. doi: 10.4103/0019-509X.118726.

●● Enlace al texto completo (gratis o de pago) [4103/0019-509X.118726](#)

AUTORES / AUTHORS: - Vishnukumar S; Umamaheswaran G; Anichavezhi D; Indumathy S; Adithan C; Srinivasan K; Kadambari D

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education & Research, Pondicherry, India.

RESUMEN / SUMMARY: - Background: Chemoresistance is an important factor determining the response of tumor to neoadjuvant chemotherapy (NACT). P-glycoprotein (P-gp) expression-mediated drug efflux is one of the mechanisms responsible for multi-drug resistance. Our study was aimed to determine the role of P-gp expression as a predictor of response to NACT in locally advanced breast cancer (LABC) patients. Materials and Methods: P-gp expression was performed by real-time quantitative polymerase chain reaction [qRT-PCR] in 76 patients with LABC. Response to adriamycin-based regimen was assessed both clinically and with contrast enhanced

computed tomography (CECT) scan before and after NACT. The significance of correlation between tumor and P-gp levels was determined with Chi-square test. Results: Twenty-one had high and 55 had low P-gp expression. On analyzing P-gp expression with response by World Health Organization (WHO) criteria, statistical significance was obtained (P = 0.038). Similarly, assessment of P-gp expression with response by Response Evaluation in Solid Tumors (RECIST) criteria in 48 patients showed statistical significance (P = 0.0005). Conclusion: This study proves that P-gp expression is a determinant factor in predicting response to NACT. Finally, detection of P-gp expression status before initiation of chemotherapy can be used as a predictive marker for NACT response and will also aid in avoiding the toxic side effects of NACT in non-responders.

[852]

TÍTULO / TITLE: - CD44 Gene Polymorphisms in Breast Cancer Risk and Prognosis: A Study in North Indian Population.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e71073. doi: 10.1371/journal.pone.0071073. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0071073](#)

AUTORES / AUTHORS: - Tulsyan S; Agarwal G; Lal P; Agrawal S; Mittal RD; Mittal B

INSTITUCIÓN / INSTITUTION: - Department of Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

RESUMEN / SUMMARY: - BACKGROUND: Cell surface biomarker CD44 plays an important role in breast cancer cell growth, differentiation, invasion, angiogenesis and tumour metastasis. Therefore, we aimed to investigate the role of CD44 gene polymorphisms in breast cancer risk and prognosis in North Indian population. MATERIALS & METHODS: A total of 258 breast cancer patients and 241 healthy controls were included in the case-control study for risk prediction. According to RECIST, 114 patients who received neo-adjuvant chemotherapy were recruited for the evaluation of breast cancer prognosis. We examined the association of tagging SNP (rs353639) of Hapmap Gujrati Indians in Houston (GIH population) in CD44 gene along with a significant reported SNP (rs13347) in Chinese population by genotyping using Taqman allelic discrimination assays. Statistical analysis was done using SPSS software, version 17. In-silico analysis for prediction of functional effects was done using F-SNP and FAST-SNP. RESULTS: No significant association of both the genetic variants of the CD44 gene polymorphisms was found with breast cancer risk. On performing univariate analysis with clinicopathological characteristics and treatment response, we found significant association of genotype (CT+TT) of rs13347 polymorphism with earlier age of onset (P = 0.029, OR = 0.037). However, significance was lost in multivariate analysis. For rs353639 polymorphism, significant association was seen with clinical tumour size,

both at the genotypic (AC+CC) ($P = 0.039$, OR = 3.02) as well as the allelic © ($P = 0.042$, OR = 2.87) levels. On performing multivariate analysis, increased significance of variant genotype ($P = 0.017$, OR = 4.29) and allele ($P = 0.025$, OR = 3.34) of rs353639 was found with clinical tumour size. In-silico analysis using F-SNP, showed altered transcriptional regulation for rs353639 polymorphism. CONCLUSIONS: These findings suggest that CD44 rs353639 genetic variants may have significant effect in breast cancer prognosis. However, both the polymorphisms- rs13347 and rs353639 had no effect on breast cancer susceptibility.

[853]

TÍTULO / TITLE: - Enhancement of natural killer cell cytotoxicity by sodium/iodide symporter gene-mediated radioiodine pretreatment in breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e70194. doi: 10.1371/journal.pone.0070194. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070194](https://doi.org/10.1371/journal.pone.0070194)

AUTORES / AUTHORS: - Kim HW; Kim JE; Hwang MH; Jeon YH; Lee SW; Lee J; Zeon SK; Ahn BC

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, Kyungpook National University School of Medicine, Daegu, Republic of Korea ; Department of Nuclear Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea.

RESUMEN / SUMMARY: - A phase II study of NK cell therapy in treatment of patients with recurrent breast cancer has recently been reported. However, because of the complexities of tumor microenvironments, effective therapeutic effects have not been achieved in NK cell therapy. Radioiodine (I-131) therapy inhibits cancer growth by inducing the apoptosis and necrosis of cancer cells. Furthermore, it can modify cancer cell phenotypes and enhance the effect of immunotherapy against cancer cells. The present study showed that I-131 therapy can modulate microenvironment of breast cancer and improve the therapeutic effect by enhancing NK cell cytotoxicity to the tumor cells. The susceptibility of breast cancer cells to NK cell was increased by precedent I-131 treatment in vitro. Tumor burden in mice treated with I-131 plus NK cell was significantly lower than that in mice treated with NK cell or I-131 alone. The up-regulation of Fas, DR5 and MIC A/B on irradiated tumor cells could be the explanation for the enhancement of NK cell cytotoxicity to tumor cells. It can be applied to breast cancer patients with iodine avid metastatic lesions that are non-responsive to conventional treatments.

[854]

TÍTULO / TITLE: - mRNA expression and hypermethylation of tumor suppressor genes apoptosis protease activating factor-1 and death-associated protein kinase in oral squamous cell carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2013 Jul;6(1):280-286. Epub 2013 May 17.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1353](#)

AUTORES / AUTHORS: - Li C; Wang L; Su J; Zhang R; Fu L; Zhou Y

INSTITUCIÓN / INSTITUTION: - Departments of Implant Center, Jilin University, Changchun, Jilin 130011, P.R. China ;

RESUMEN / SUMMARY: - Apoptosis protease activating factor-1 (Apaf-1) and death-associated protein kinase (DAPK) are p53 pathway-related genes that play significant roles in the activation of caspases, which are involved in mitochondrial-mediated apoptosis. The present study aimed to confirm the role of hyper-methylation of the Apaf-1 and DAPK gene promoter regions in oral squamous cell carcinoma (OSCC) and the effect of the demethylation drug, 5-aza-2'-deoxycytidine (DAC). mRNA from 53 OSCC samples, 23 normal oral mucosa samples and Tca8113 human tongue carcinoma cell lines was detected using semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR). The DNA from each sample was analyzed using methylation-specific PCR (MSP). The Tca8113 cells were demethylated using DAC and the demethylation and re-expression of Apaf-1 and DAPK were analyzed. The Apaf-1 and DAPK mRNA expression index was decreased in 51 (96.23%) and 50 (94.34%) cases, respectively, in the tumor tissues. Hypermethylation of the Apaf-1 and DAPK promoter regions was detected in 46 (86.79%) and 38 (71.69%) cases, respectively. Promoter hypermethylation of the two genes correlated with a decreased mRNA expression in the tumor tissues. Subsequent to being treated with DAC, Apaf-1 and DAPK were demethylated and re-expressed in the Tca8113 cells. Apaf-1 and DAPK promoter hypermethylation may be associated with low gene expression in OSCC. Furthermore, a loss of Apaf-1 and DAPK expression may recover following demethylation. The data provide evidence that methylation exists in OSCC and may play a role in the development of this disease.

[855]

TÍTULO / TITLE: - The proteasome inhibitor bortezomib inhibits the growth of canine malignant melanoma cells in vitro and in vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Vet J. 2013 Aug 11. pii: S1090-0233(13)00378-X. doi: 10.1016/j.tvjl.2013.08.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.tvjl.2013.08.003](#)

AUTORES / AUTHORS: - Ito K; Kobayashi M; Kuroki S; Sasaki Y; Iwata T; Mori K; Kuroki T; Ozawa Y; Tetsuka M; Nakagawa T; Hiroi T; Yamamoto H; Ono K; Washizu T; Bonkobara M

INSTITUCIÓN / INSTITUTION: - Department of Veterinary Clinical Pathology, Nippon Veterinary and Life Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 180-8602, Japan.

RESUMEN / SUMMARY: - Canine malignant melanomas are highly aggressive and fatal neoplasms. In the present report, 21 drugs that target specific signalling pathways were screened for their growth inhibitory activity on three canine malignant melanoma cell lines. The proteasome inhibitor bortezomib inhibited the growth of these cell lines. The growth inhibitory properties of bortezomib were then examined using nine canine malignant melanoma cell lines. Bortezomib demonstrated potent growth inhibitory activity in all cell lines with calculated IC50 values of 3.5-5.6nM. Because suppression of the NF-kappaB pathway by preventing proteasomic degradation of I kappa B is an important mechanism of the anti-tumour activity of bortezomib, the activation status of and the effect of bortezomib on the NF-kappaB pathway were examined using a canine malignant melanoma cell line, CMM-1. The NF-kappaB pathway was constitutively activated in CMM-1 cells and bortezomib efficiently suppressed this activated pathway. Using a CMM-1 xenograft mouse model, bortezomib also significantly inhibited tumour growth via suppression of tumour cell proliferation. Collectively, these findings suggest that bortezomib has growth inhibitory activity against canine malignant melanomas potentially through suppression of the constitutively activated NF-kappaB pathway. Targeted therapy using bortezomib could therefore be beneficial in the management of canine malignant melanomas.

[856]

TÍTULO / TITLE: - Leflunomide reduces proliferation and induces apoptosis in neuroblastoma cells in vitro and in vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 9;8(8):e71555. doi: 10.1371/journal.pone.0071555.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071555](https://doi.org/10.1371/journal.pone.0071555)

AUTORES / AUTHORS: - Zhu S; Yan X; Xiang Z; Ding HF; Cui H

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Silkworm Genome Biology, Southwest University, Chongqing, China ; College of Life Science, Southwest University, Chongqing, China.

RESUMEN / SUMMARY: - Leflunomide as an immunosuppressive drug is generally used in the treatment of rheumatoid arthritis. It inhibits DHODH (dihydroorotate dehydrogenase), which is one of the essential enzymes in the de novo pyrimidine biosynthetic pathway. Here we showed that leflunomide significantly reduced cell proliferation and self-renewal activity. Annexin V-FITC/PI staining assay revealed that leflunomide induced S-phase cell cycle arrest, and promoted cell apoptosis. In vivo xenograft study in SCID mice showed that leflunomide inhibited tumor growth and development. We also observed that DHODH was commonly expressed in neuroblastoma. When treated with leflunomide, the neuroblastoma cell lines BE(2)-C,

SK-N-DZ, and SK-N-F1 showed dramatic inhibition of DHODH at mRNA and protein levels. Considering the favorable toxicity profile and the successful clinical experience with leflunomide in rheumatoid arthritis, this drug represents a potential new candidate for targeted therapy in neuroblastoma.

[857]

TÍTULO / TITLE: - Prognostic Value of CD109+ Circulating Endothelial Cells in Recurrent Glioblastomas Treated with Bevacizumab and Irinotecan.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 12;8(9):e74345. doi: 10.1371/journal.pone.0074345.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074345](https://doi.org/10.1371/journal.pone.0074345)

AUTORES / AUTHORS: - Cuppini L; Calleri A; Bruzzone MG; Prodi E; Anghileri E; Pellegatta S; Mancuso P; Porrati P; Di Stefano AL; Ceroni M; Bertolini F; Finocchiaro G; Eoli M

INSTITUCIÓN / INSTITUTION: - Department of Neuro-Oncology Unit, Fondazione IRCCS Istituto Neurologico C, Besta, Milan, Italy.

RESUMEN / SUMMARY: - BACKGROUND: Recent data suggest that circulating endothelial and progenitor cells (CECs and CEPs, respectively) may have predictive potential in cancer patients treated with bevacizumab, the antibody recognizing vascular endothelial growth factor (VEGF). Here we report on CECs and CEPs investigated in 68 patients affected by recurrent glioblastoma (rGBM) treated with bevacizumab and irinotecan and two Independent Datasets of rGBM patients respectively treated with bevacizumab alone (n=32, independent dataset A: IDA) and classical antineoplastic chemotherapy (n=14, independent dataset B: IDB). METHODS: rGBM patients with KPS \geq 50 were treated until progression, as defined by MRI with RANO criteria. CECs expressing CD109, a marker of tumor endothelial cells, as well as other CEC and CEP subtypes, were investigated by six-color flow cytometry. RESULTS: A baseline count of CD109+ CEC higher than 41.1/ml (1(st) quartile) was associated with increased progression free survival (PFS; 20 versus 9 weeks, P=0.008) and overall survival (OS; 32 versus 23 weeks, P=0.03). Longer PFS (25 versus 8 weeks, P=0.02) and OS (27 versus 17 weeks, P=0.03) were also confirmed in IDA with CD109+ CECs higher than 41.1/ml but not in IDB. Patients treated with bevacizumab with or without irinotecan that were free from MRI progression after two months of treatment had significant decrease of CD109+ CECs: median PFS was 19 weeks; median OS 29 weeks. The presence of two non-contiguous lesions (distant disease) at baseline was an independent predictor of shorter PFS and OS (P<0.001). CONCLUSIONS: Data encourage further studies on the predictive potential of CD109+ CECs in GBM patients treated with bevacizumab.

[858]

TÍTULO / TITLE: - Riccardin D Exerts Its Antitumor Activity by Inducing DNA Damage in PC-3 Prostate Cancer Cells In Vitro and In Vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 17;8(9):e74387. doi: 10.1371/journal.pone.0074387.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074387](https://doi.org/10.1371/journal.pone.0074387)

AUTORES / AUTHORS: - Hu Z; Kong F; Si M; Tian K; Yu LX; Young CY; Yuan H; Lou H

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RESUMEN / SUMMARY: - We recently reported that Riccardin D (RD) was able to induce apoptosis by targeting Topo II. Here, we found that RD induced cell cycle arrest in G2/M phase in PC-3 cells, and caused remarkable DNA damage as evidenced by induction of gammaH2AX foci, micronuclei, and DNA fragmentation in Comet assay. Time kinetic and dose-dependent studies showed that ATM/Chk2 and ATR/Chk1 signaling pathways were sequentially activated in response to RD. Blockage of ATM/ATR signaling led to the attenuation of RD-induced gammaH2AX, and to the partial recovery of cell proliferation. Furthermore, RD exposure resulted in the inactivation of BRCA1, suppression of HR and NHEJ repair activity, and downregulation of the expressions and DNA-end binding activities of Ku70/86. Consistent with the observations, microarray data displayed that RD triggered the changes in genes responsible for cell proliferation, cell cycle, DNA damage and repair, and apoptosis. Administration of RD to xenograft mice reduced tumor growth, and coordinately caused alterations in the expression of genes involved in DNA damage and repair, along with cell apoptosis. Thus, this finding identified a novel mechanism by which RD affects DNA repair and acts as a DNA damage agent in prostate cancer.

[859]

TÍTULO / TITLE: - The receptor AXL diversifies EGFR signaling and limits the response to EGFR-targeted inhibitors in triple-negative breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Sci Signal. 2013 Aug 6;6(287):ra66. doi: 10.1126/scisignal.2004155.

●● Enlace al texto completo (gratis o de pago) [1126/scisignal.2004155](https://doi.org/10.1126/scisignal.2004155)

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RESUMEN / SUMMARY: - The relationship between drug resistance, changes in signaling, and emergence of an invasive phenotype is well appreciated, but the underlying mechanisms are not well understood. Using machine learning analysis applied to the Cancer Cell Line Encyclopedia database, we identified expression of AXL, the gene that encodes the epithelial-to-mesenchymal transition (EMT)-associated receptor tyrosine kinase (RTK) AXL, as exceptionally predictive of lack of response to ErbB family receptor-targeted inhibitors. Activation of EGFR (epidermal growth factor receptor)

transactivated AXL, and this ligand-independent AXL activity diversified EGFR-induced signaling into additional downstream pathways beyond those triggered by EGFR alone. AXL-mediated signaling diversification was required for EGF (epidermal growth factor)-elicited motility responses in AXL-positive TNBC (triple-negative breast cancer) cells. Using cross-linking coimmunoprecipitation assays, we determined that AXL associated with EGFR, other ErbB receptor family members, MET (hepatocyte growth factor receptor), and PDGFR (platelet-derived growth factor receptor) but not IGF1R (insulin-like growth factor 1 receptor) or INSR (insulin receptor). From these AXL interaction data, we predicted AXL-mediated signaling synergy for additional RTKs and validated these predictions in cells. This alternative mechanism of receptor activation limits the use of ligand-blocking therapies and indicates against therapy withdrawal after acquired resistance. Further, subadditive interaction between EGFR- and AXL-targeted inhibitors across all AXL-positive TNBC cell lines may indicate that increased abundance of EGFR is principally a means to transactivation-mediated signaling.

[860]

TÍTULO / TITLE: - Combination Therapy with the Histone Deacetylase Inhibitor LBH589 and Radiation Is an Effective Regimen for Prostate Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 26;8(8):e74253. doi: 10.1371/journal.pone.0074253.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074253](https://doi.org/10.1371/journal.pone.0074253)

AUTORES / AUTHORS: - Xiao W; Graham PH; Hao J; Chang L; Ni J; Power CA; Dong Q; Kearsley JH; Li Y

INSTITUCIÓN / INSTITUTION: - Cancer Care Centre and Prostate Cancer Institute, St George Hospital, Kogarah, New South Wales, Australia ; Faculty of Medicine, University of New South Wales, Kensington, New South Wales, Australia ; Department of Radiation Oncology, Cancer Centre, Sun Yat-sen University, Guangzhou, Guangdong, China ; State Key Laboratory of Oncology in Southern China, Guangzhou, Guangdong, China.

RESUMEN / SUMMARY: - Radiation therapy (RT) continues to be one of the most popular treatment options for localized prostate cancer (CaP). The purpose of the study was to investigate the in vitro effect of LBH589 alone and in combination with RT on the growth and survival of CaP cell lines and the possible mechanisms of radiosensitization of this combination therapy. The effect of LBH589 alone or in combination with RT on two CaP cell lines (PC-3 and LNCaP) and a normal prostatic epithelial cell line (RWPE-1) was studied by MTT and clonogenic assays, cell cycle analysis, western blotting of apoptosis-related and cell check point proteins, and DNA double strand break (DSB) repair markers. The immunofluorescence staining was used to further confirm DSB expression in treated CaP cells. Our results indicate that LBH589 inhibited proliferation in both CaP and normal prostatic epithelial cells in a time-and-dose-dependent manner; low-dose of LBH589 (IC20) combined with RT greatly improved efficiency of

cell killing in CaP cells; compared to RT alone, the combination treatment with LBH589 and RT induced more apoptosis and led to a steady increase of sub-G1 population and abolishment of RT-induced G2/M arrest, increased and persistent DSB, less activation of non-homologous end joining (NHEJ)/homologous recombination (HR) repair pathways and a panel of cell cycle related proteins. These results suggest that LBH589 is a potential agent to increase radiosensitivity of human CaP cells. LBH589 used either alone, or in combination with RT is an attractive strategy for treating human CaP.

[861]

TÍTULO / TITLE: - Boron neutron capture therapy induces cell cycle arrest and cell apoptosis of glioma stem/progenitor cells in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Radiat Oncol. 2013 Aug 6;8(1):195. doi: 10.1186/1748-717X-8-195.

●● Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-195](#)

AUTORES / AUTHORS: - Sun T; Zhang Z; Li B; Chen G; Xie X; Wei Y; Wu J; Zhou Y; Du Z

INSTITUCIÓN / INSTITUTION: - Neurosurgery & Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China.

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RESUMEN / SUMMARY: - BACKGROUND: Glioma stem cells in the quiescent state are resistant to clinical radiation therapy. An almost inevitable glioma recurrence is due to the persistence of these cells. The high linear energy transfer associated with boron neutron capture therapy (BNCT) could kill quiescent and proliferative cells. METHODS: The present study aimed to evaluate the effects of BNCT on glioma stem/progenitor cells in vitro. The damage induced by BNCT was assessed using cell cycle progression, apoptotic cell ratio and apoptosis-associated proteins expression. RESULTS: The surviving fraction and cell viability of glioma stem/progenitor cells were decreased compared with differentiated glioma cells using the same boronophenylalanine pretreatment and the same dose of neutron flux. BNCT induced cell cycle arrest in the G2/M phase and cell apoptosis via the mitochondrial pathway, with changes in the expression of associated proteins. CONCLUSIONS: Glioma stem/progenitor cells, which are resistant to current clinical radiotherapy, could be effectively killed by BNCT in vitro via cell cycle arrest and apoptosis using a prolonged neutron irradiation, although radiosensitivity of glioma stem/progenitor cells was decreased compared with differentiated glioma cells when using the same dose of thermal neutron exposure and boronophenylalanine pretreatment. Thus, BNCT could offer an appreciable therapeutic advantage to prevent tumor recurrence, and may become a promising treatment in recurrent glioma.

[862]

TÍTULO / TITLE: - Prognostic importance of cyclin E1 expression in neuroblastic tumors in children.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pol J Pathol. 2013;64(2):149-52.

AUTORES / AUTHORS: - Taran K; Owecka A; Kobos J

INSTITUCIÓN / INSTITUTION: - Katarzyna Taran MD, PhD, Department of Pathology, Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland, e-mail:

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RESUMEN / SUMMARY: - A number of studies have indicated that cyclin E plays an important role in a variety of neoplastic processes. In our study we evaluated cyclin E1 expression and the possible prognostic value of this protein in neuroblastic tumors in children. Cyclin E1 expression was investigated by means of immunohistochemical analysis of 25 neuroblastic tumor tissue samples. We found a significant correlation between high cyclin E1 expression and deaths due to neoplastic disease. The mean values of cyclin E1 indexes in fatal cases were twice as high as in other cases. The results indicate that high cyclin E1 expression may have prognostic importance in neuroblastic tumors in children.

[863]

TÍTULO / TITLE: - Treating cancer with heat: hyperthermia as promising strategy to enhance apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Pak Med Assoc. 2013 Apr;63(4):504-8.

AUTORES / AUTHORS: - Ahmed K; Zaidi SF

INSTITUCIÓN / INSTITUTION: - Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, Pakistan. kanwalahd@gmail.com

RESUMEN / SUMMARY: - The fundamental idea and the effects of heat on cancer cells are well known. However, the results obtained in therapy by hyperthermia (HT) alone have been only partially satisfactory. Treatment at temperatures between .40 and 44 degrees C is cytotoxic for cells in an environment with a low oxygen partial pressure and low pH, conditions that are found specifically within tumour tissue, due to insufficient blood perfusion. Under such conditions radiotherapy is less effective, and systemically applied cytotoxic agents will reach such areas in lower concentrations than in well-perfused areas. Therefore, clinically, it is preferred to use hyperthermia in combination with radiation therapy and chemotherapy. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources; regional hyperthermia by perfusion of organs or limbs, or by irrigation of body cavities; and whole-body hyperthermia. Number of studies have reported the combination of thermo-radiotherapy. Consequently, much attention has been focussed on identifying agents among the conventional chemotherapeutic substances that can sensitise tumour cells to hyperthermia-induced damage with minimal effects on normal cells. In

this review, we overviewed important mechanisms of hyperthermia-induced apoptosis and the substances which can act as heat sensitizers in cancer therapy.

[864]

TÍTULO / TITLE: - An oncolytic adenovirus expressing interleukin-24 enhances antitumor activities in combination with paclitaxel in breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Nov;8(5):1416-1424. doi: 10.3892/mmr.2013.1680. Epub 2013 Sep 13.

●● [Enlace al texto completo \(gratis o de pago\) 3892/mmr.2013.1680](#)

AUTORES / AUTHORS: - Fang L; Cheng Q; Bai J; Qi YD; Liu JJ; Li LT; Zheng JN

INSTITUCIÓN / INSTITUTION: - Jiangsu Key Laboratory of Biological Cancer Therapy, Xuzhou Medical College, Xuzhou, Jiangsu 221002, P.R. China.

RESUMEN / SUMMARY: - Oncolytic adenoviruses are a novel class of anticancer treatment, based upon their ability to replicate selectively within malignant cells resulting in cell lysis. The replicationselective adenovirus, ZD55IL24, was constructed by harboring an E1B55 kDa deletion and arming with interleukin-24 (IL-24). The microtubulestabilizing drug paclitaxel (PTX) exhibits activity in relapsed cancer. In the present study, the synergistic antitumor effects of the combination of PTX and ZD55IL24 on breast cancer cells was investigated. The results demonstrated that there were different roles for PTX in the expression of transgenic mRNA and protein. ZD55IL24 combined with PTX induced marked growth inhibition of MDAMB231 and Bcap37 cells. PTX increased viral uptake and appeared not to alter the replication of ZD55IL24 in breast cancer cells. Annexin Vfluorescein isothiocyanate/propidium iodide staining and the Hoechst 33258 assay indicated that ZD55IL24 induced an increase in the number of apoptotic cells when administered in combination with PTX. It was demonstrated that ZD55IL24 conjugated with PTX was highly concomitant, and increased proapoptotic proteins levels, activated caspase3, -7 and -9 and downregulated antiapoptotic proteins. These results suggested that ZD55IL24 in combination with PTX exhibited a markedly increased cytotoxic and apoptosisinducing effect in breast cancer cells. Thus, this chemogeneviro therapeutic strategy was demonstrated to be superior to conventional chemotherapy or geneviro therapy alone.

[865]

TÍTULO / TITLE: - Tracking in vivo migration and distribution of antigen-specific cytotoxic T lymphocytes by 5,6-carboxyfluorescein diacetate succinimidyl ester staining during cancer immunotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin Med J (Engl). 2013 Aug;126(16):3019-25.

AUTORES / AUTHORS: - Xu WL; Li SL; Wen M; Wen JY; Han J; Zhang HZ; Gao F; Cai JH

INSTITUCIÓN / INSTITUTION: - Department of Pediatric Surgery, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, China (Email: drxwl99@126.com).

RESUMEN / SUMMARY: - BACKGROUND: Killing of targeted tumors during adoptive cell transfer therapy is associated with cytotoxic T lymphocyte (CTL) numbers, immunophenotype, tumor-specificity, and in vivo residence time, migration, and distribution. Therefore, tracing in vivo persistence, migration, and distribution of CTLs is important for cancer immunotherapy. METHODS: Optimal staining concentration for CTL proliferation was determined by cell counting kit-8 (CCK-8) assay and killing efficiencies of CTLs or carboxyfluorescein diacetate succinimidyl ester (CFSE)-labeled melanoma antigen-specific cytotoxic T lymphocytes (CFSE-CTLs) for malignant melanoma cells in vitro were compared. Additionally, CFSE-CTLs were intravenously transfused to mice receiving B16 melanoma, and their residence time, migration, and distribution in vivo were observed by measuring fluorescence intensities of CFSE-CTLs per gram of tissue (%FI/g) in various tissues and analyzing tumor/non-tumor (T/NT) values. Anti-tumor effects of transferred CTLs and correlation between %FI/g and D-value of tumor size were analyzed. RESULTS: Five-micromolar CFSE was optimal for labeling CTLs with minimal cytotoxicity. No significant difference occurred between CTLs and CFSE-CTLs for tumor cell killing ($P = 0.849$) or interleukin-2 ($P = 0.318$) and interferon-gamma ($P = 0.201$) levels. Distribution of CTLs in vivo varied with time. A negative correlation between %FI/g in tumors and D-value of tumor sizes by Spearman correlation analysis was observed. CTLs were recruited to and killed tumors from 6 hours to 3 days after cell infusion. CTLs were observed up to three weeks later in the tumor, liver, kidneys, and spleen; this was related to the abundant blood supply or the nature of immune organs. CONCLUSIONS: CCK-8 assay is a novel method to select optimal CFSE staining concentrations. Fluorescence intensity of transferred CTLs reflects their killing efficiency of tumors. CFSE fluorescent markers can trace in vivo CTL persistence, migration, and distribution because of its stability, long half-life, and low toxicity.

[866]

TÍTULO / TITLE: - Clinical significance and prognostic value of pentraxin-3 as serologic biomarker for lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(7):4215-21.

AUTORES / AUTHORS: - Zhang D; Ren WH; Gao Y; Wang NY; Wu WJ

INSTITUCIÓN / INSTITUTION: - Department of Clinical Laboratory, the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China E-mail : ren_weihong@hotmail.com.

RESUMEN / SUMMARY: - Purposes: Lung cancer is prevalent worldwide and improvements in timely and effective diagnosis are need. Pentraxin-3 as a novel serum marker for lung cancer (LC) has not been validated in large cohort studies. The aim of the study was to assess its clinical value in diagnosis and prognosis. Methods: We analyzed serum PTX-3 levels in a total of 1,605 patients with LC, benign lung diseases and healthy controls, as well as 493 non- lung cancer patients including 12 different types of cancers. Preoperative and postoperative data were further assessed in patients undergoing LC resection. The diagnostic performance of PTX-3 for LC and early-stage LC was assessed using receiver operating characteristics (ROC) by comparing with serum carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA 21-1). Results: Levels of PTX-3 in serum were significantly higher in patients with LC than all controls. ROC curves showed the optimum diagnostic cutoff was 8.03ng/mL (AUC 0.823, [95%CI 0.789-0.856], sensitivity 72.8%, and specificity 77.3% in the test cohort; 0.802, [95%CI 0.762-0.843], sensitivity 69.7%, and specificity 76.4% in the validate cohort). Similar diagnostic performance of PTX-3 was observed for early-stage LC. PTX-3 decreased following surgical resection of LC and increased with tumor recurrence. Significantly elevated PTX-3 levels were also seen in patients with non-lung cancers. Conclusions: The present data revealed that PTX-3 was significantly increased in both tissue and serum samples in LC patients. PTX-3 is a valuable biomarker for LC and improved identification of patients with LC and early-stage LC from those with non-malignant lung diseases.

[867]

TÍTULO / TITLE: - VDAC1-based peptides: novel pro-apoptotic agents and potential therapeutics for B-cell chronic lymphocytic leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 19;4:e809. doi: 10.1038/cddis.2013.316.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.316](#)

AUTORES / AUTHORS: - Prezma T; Shteinfer A; Admoni L; Raviv Z; Sela I; Levi I; Shoshan-Barmatz V

INSTITUCIÓN / INSTITUTION: - Department of Life Sciences and the National Institute for Biotechnology in the Negev, BeerSheva, Israel.

RESUMEN / SUMMARY: - The voltage-dependent anion channel 1 (VDAC1), localized in the outer mitochondrial membrane, mediates metabolic cross-talk between the mitochondrion and the cytoplasm and thus serves a fundamental role in cell energy metabolism. VDAC1 also plays a key role in mitochondria-mediated apoptosis, interacting with anti-apoptotic proteins. Resistance of cancer cells to apoptosis involves quenching the mitochondrial apoptotic pathway by over-expression of anti-apoptotic/pro-survival hexokinase (HK) and Bcl-2 family proteins, proteins that mediate their anti-apoptotic activities via interaction with VDAC1. Using specifically

designed VDAC1-based cell-penetrating peptides, we targeted these anti-apoptotic proteins to prevent their pro-survival/anti-apoptotic activities. Anti-apoptotic proteins are expressed at high levels in B-cell chronic lymphocytic leukemia (CLL), an incurable disease requiring innovative new approaches to improve therapeutic outcome. CLL is characterized by a clonal accumulation of mature neoplastic B cells that are resistant to apoptosis. Specifically, we demonstrate that the VDAC1-based peptides (Antp-LP4 and N-Terminal-Antp) selectively kill peripheral blood mononuclear cells (PBMCs) obtained from CLL patients, yet spare those obtained from healthy donors. The cell death induction competence of the peptides was well correlated with the amount of double positive CD19/CD5 cancerous CLL PBMCs, further illustrating their selectivity toward cancer cells. Moreover, these VDAC1-based peptides induced apoptosis by activating the mitochondria-mediated pathway, reflected in membrane blebbing, condensation of nuclei, DNA fragmentation, release of mitochondrial cytochrome c, loss of mitochondrial membrane potential, decreased cellular ATP levels and detachment of HK, all leading to apoptotic cell death. Thus, the mode of action of the peptides involves decreasing energy production and inducing apoptosis. Over 27 versions of cell-penetrating VDAC1-based peptides were designed and screened to identify the most stable, short and apoptosis-inducing peptides toward CLL-derived lymphocytes. In this manner, three optimized peptides suitable for in vivo studies were identified. This study thus reveals the potential of VDAC1-based peptides as an innovative and effective anti-CLL therapy.

[868]

TÍTULO / TITLE: - Inhibition of nuclear factor-kappaB activity enhanced chemosensitivity to cisplatin in human lung adeno-carcinoma A549 cells under chemical hypoxia conditions.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin Med J (Engl). 2013 Sep;126(17):3276-82.

AUTORES / AUTHORS: - Li F; Huang L; Su XL; Gu QH; Hu CP

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, Xiangya Hospital, Central South University, Changsha, Hunan 410007, China.

RESUMEN / SUMMARY: - BACKGROUND: Tumor hypoxia, one of the features of solid tumors, is associated with chemo-resistance. Recently, nuclear factor-kappaB (NF-kappaB) was found to be activated during hypoxia. However, the impact of NF-kappaB activation on chemo-resistance during hypoxia remains unknown. METHODS: Human lung adenocarcinoma A549 cells were transfected with NF-kappaB p65siRNA and treated with cobalt chloride (CoCl₂) to mimic hypoxia in the presence or absence of cisplatin. NF-kappaB expression was measured by Western blotting, immune-fluorescence and real-time PCR. Hypoxia-inducible factor-1alpha (HIF-1alpha) and Bcl-2 expression were determined by Western blotting. Cell apoptosis and survival with half-maximum inhibitory concentration (IC₅₀) of cisplatin were determined by Annexin V-

FITC/PI and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT), respectively. RESULTS: Exposure of A549 cells to CoCl₂ increased nuclear HIF-1^α protein expression, and enhanced NF-kappaB p65 protein nuclear accumulation (the mark of NF-kappaB activation) in a time and dose dependant manner. CoCl₂ did not promote apoptosis in A549 cells; on the contrary, it reduced cisplatin-induced apoptosis and increased the IC50 of cisplatin. However, when we inhibited CoCl₂-induced activation of NF-kappaB through NF-kappaB p65siRNA, cisplatin-induced apoptosis was increased and IC50 of cisplatin was reduced to levels similar to those in control cells. Meanwhile, CoCl₂-induced Bcl-2 overexpression was down-regulated in the presence of cisplatin when NF-kappaB activity was inhibited. CONCLUSION: Up-regulating Bcl-2 might be involved in NF-kappaB activation induced resistance to cisplatin in A549 cells under CoCl₂-induced chemical hypoxia.

[869]

TÍTULO / TITLE: - Towards the goal of personalized medicine in gastric cancer—time to move beyond HER2 inhibition. Part II: Targeting gene mutations and gene amplifications and the angiogenesis pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Discov Med. 2013 Aug;16(86):7-14.

AUTORES / AUTHORS: - Lee J; Ou SH

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Samsung Medical Center, SungKyunKwan University School of Medicine, Seoul, 135-710, South Korea.

RESUMEN / SUMMARY: - Gastric cancer is the second leading cancer cause of death globally. Apart from the successful targeting of HER2 over-expression in gastric cancer (GC) with trastuzumab, other targeted therapies in GC have fallen short or still in early clinical development. While HER2 over-expression accounts for up to 20% of GC, other potential actionable driver mutations occur at a much lower frequency in GC. In this review we describe some of the more interesting genetic aberrations including driver mutations in gastric cancer that have very potent inhibitors against them already in clinical development. Part I of this review will concentrate on the receptor tyrosine kinase (RTK) gene amplification (HER2, FGFR2, MET, EGFR). Part II will concentrate on gene mutations (HER2, KRAS, PIK3CA, BRAF) and gene rearrangement (ROS1, BRAF, HER2). Because of the low frequency of these potential driver mutations, perseverance in screening for these mutations will be needed in order to enroll enough of each uniquely molecularly defined subset of GC in order to demonstrate significant clinical benefit in a unique molecularly targeted therapy trial. This approach has been successfully employed in the clinical approval of crizotinib for the treatment of ALK-rearranged non-small cell lung cancer. Finally, we discuss a paradigm shift in the personalized treatment of GC patients where multiplex comprehensive screening of all

GC patients for all these potential driver mutations simultaneously is performed to achieve efficiencies and timeliness in diagnosis and allowing enrollment into different molecularly targeted therapy trials and the prospective discovery of novel yet unknown actionable driver mutations.

[870]

TÍTULO / TITLE: - Value of pre-treatment biomarkers in prediction of response to neoadjuvant endocrine therapy for hormone receptor-positive postmenopausal breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin J Cancer Res. 2013 Aug;25(4):397-404. doi: 10.3978/j.issn.1000-9604.2013.08.01.

●● [Enlace al texto completo \(gratis o de pago\) 3978/j.issn.1000-9604.2013.08.01](#)

AUTORES / AUTHORS: - Ying M; He Y; Qi M; Dong B; Lu A; Li J; Xie Y; Wang T; Ouyang T

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Breast Cancer Center, Peking University Cancer Hospital & Institute, Beijing 100142, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To determine the predictive ability of biomarkers for responses to neoadjuvant endocrine therapy (NET) in postmenopausal breast cancer. **METHODS:** Consecutive 160 postmenopausal women with T1-3N0-1M0 hormone receptor (HR)-positive invasive breast cancer were treated with anastrozole for 16 weeks before surgery. New slides of tumor specimens taken before and after treatment were conducted centrally for biomarker analysis and classified using the Applied Imaging Ariol MB-8 system. The pathological response was evaluated using the Miller & Payne classification. The cell cycle response was classified according to the change in the Ki67 index after treatment. Multivariable logistic regression analysis was used to calculate the combined index of the biomarkers. Receiver operating characteristic (ROC) curves were used to determine whether parameters may predict response. **RESULTS:** The correlation between the pathological and cell cycle responses was low (Spearman correlation coefficient =0.241, P<0.001; Kappa value =0.119, P=0.032). The cell cycle response was significantly associated with pre-treatment estrogen receptor (ER) status (P=0.001), progesterone receptor (PgR) status (P<0.001), human epidermal growth factor receptor 2 (Her-2) status (P=0.050) and the Ki67 index (P<0.001), but the pathological response was not correlated with these factors. Pre-treatment ER levels [area under the curve (AUC) =0.634, 95% confidence interval (95% CI), 0.534-0.735, P=0.008] and combined index of pre-treatment ER and PgR levels (AUC =0.684, 95% CI, 0.591-0.776, P<0.001) could not predict the cell cycle response, but combined index including per-treatment ER/PR/Her-2/Ki67 expression levels could (AUC =0.830, 95% CI, 0.759-0.902, P<0.001). **CONCLUSIONS:** The combined use of pre-

treatment ER/PgR/Her-2/Ki67 expression levels, instead of HR expression levels, may predict the cell cycle response to NET.

[871]

TÍTULO / TITLE: - Efficacy of Liposomal Monensin on the Enhancement of the Antitumour Activity of Liposomal Ricin in Human Epidermoid Carcinoma (KB) Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Indian J Pharm Sci. 2013 Jan;75(1):16-22. doi: 10.4103/0250-474X.113533.

●● [Enlace al texto completo \(gratis o de pago\) 4103/0250-474X.113533](#)

AUTORES / AUTHORS: - Tyagi N; Rathore SS; Ghosh PC

INSTITUCIÓN / INSTITUTION: - Department of Oncologic Sciences, Mitchel Cancer Institute, University of South Alabama, Mobile, Alabama, USA.

RESUMEN / SUMMARY: - The monensin, known to enhance the cytotoxicity of ricin and ricin-based immunotoxins is a very hydrophobic molecule and this limits its administration in optimum doses under in vivo conditions. In order to realise its full potential, monensin was intercalated into various liposomal formulations and its ability to potentiate the cytotoxicity of ricin liposomes in human epidermoid carcinoma (KB) cells was studied. It was observed that ricin cytotoxicity enhancing ability of monensin liposome depends on the surface charge as well as density and chain length of distearoyl phosphatidylethanolamine-methoxy polyethylene glycol present on the surface of liposomal monensin. Maximum potentiation on the cytotoxicity of liposomal ricin was observed by monensin entrapped in neutral liposome (106.5 fold) followed by negatively charged (94.2 fold) and positively charged liposome (90 fold). Studies on the effect of variation of density and chain length of distearoyl phosphatidylethanolamine-methoxy polyethylene glycol showed that neutral monensin liposomes having 2.5 mol% distearoyl phosphatidylethanolamine-methoxy polyethylene glycol with chain length of 2000 exhibits maximum potentiation (117.6 fold) on the cytotoxicity of ricin liposomes when the cellular uptake of monensin liposome was maximum (42.0%) and the zeta potential value on the surface of liposomes was -0.645. The present study has clearly shown that liposomal monensin is very effective in enhancing the cytotoxicity of liposomal ricin in human cancer cells and liposome can be used as in vivo deliver vehicle for monensin to potentiate the cytotoxicity of liposomal ricin to eliminate cancer cells.

[872]

TÍTULO / TITLE: - Gene expression profiling of non-hodgkin lymphomas.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(7):4393-8.

AUTORES / AUTHORS: - Zekri AR; Hassan ZK; Bahnassy AA; Eldahshan DH; El-Rouby MN; Kamel MM; Hafez MM

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RESUMEN / SUMMARY: - Background: Chromosomal translocations are genetic aberrations associated with specific non-Hodgkin lymphoma (NHL) subtypes. This study investigated the differential gene expression profile of Egyptian NHL cases based on a microarray approach. Materials and Methods: The study included tissue samples from 40 NHL patients and 20 normal lymph nodes used as controls. Total RNA was extracted and used for cDNA microarray assays. The quantitative real time polymerase chain reaction was used to identify the aberrantly expressed genes in cancer. Results: Significant associations of 8 up-regulated and 4 down-regulated genes with NHL were observed. Aberrant expression of a new group of genes not reported previously was apparent, including down-regulated NAG14 protein, 3 beta hydroxy-delta 5-c27 steroid oxi-reductase, oxi-glutarate dehydrogenase (lipo-amide), immunoglobulin lambda like polypeptide 3, protein kinase x linked, Hmt1, and caveolin 2 Tetra protein. The up-regulated genes were Rb binding protein 5, DKFZP586J1624 protein, protein kinase inhibitor gamma, zinc finger protein 3, choline ethanolamine phospho-transferase CEPT1, protein phosphatase, and histone deacetylase-3. Conclusions: This study revealed that new differentially expressed genes that may be markers for NHL patients and individuals who are at high risk for cancer development.

[873]

TÍTULO / TITLE: - MALT lymphomas -Treated with chemotherapy or radiotherapy: Clinical Features, Prognostic factors and Survival.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Gulf J Oncolog. 2013 Jul;1(14):76-80.

AUTORES / AUTHORS: - Alshemmari S; Sreedharan PS; Krishnan Y

INSTITUCIÓN / INSTITUTION: - Dr Salem Al Shemmari, Chairman, Dept. of Medical Oncology, Sheikha Badriya Al Sabah Centre, Kuwait Cancer Control Center, Kuwait. Phone:965- 66670090, Email: salem61@gmail.com.

RESUMEN / SUMMARY: - Objective: MALT lymphomas are a group of extranodal indolent lymphomas that usually present as stage IE. To clarify clinical features, treatment alternatives and outcomes, we evaluated 38 patients treated with chemotherapy or radiotherapy between 2000 and 2011. Patients and Methods: MALT lymphoma patients identified according to WHO classification and treated at KCCC between 2000 and 2011 were included in this study. Demographic and clinical data are presented as means or medians. Overall survival was estimated using the Kaplan-Meier method. Survival rates were compared using the log-rank test. A p value < 0.05 was considered

significant. Results: The median age of the patients was 49 years and the male to female ratio was 2:1. Gastric MALT accounted for 63% of all patients and the most common presenting symptom was abdomen pain and dyspepsia. The common extra gastric sites were salivary glands, lung and orbit. 90% of the patients presented with early stage disease. Two patients had history of pre-existing autoimmune disease. Even among patients who had failed prior antibiotic therapy for Helicobacter pylori, treatment with chemotherapy achieved good results with 5 year survival of 80%. Conclusion: MALT lymphomas are indolent neoplasm's with excellent long term outcome. There is no significant difference in survival between gastric and extra-gastric MALT lymphoma. Keywords: MALT lymphoma, Gastric Neoplasm, H. pylori.

[874]

TÍTULO / TITLE: - Enhanced levels of double-strand DNA break repair proteins protect ovarian cancer cells against genotoxic stress-induced apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Ovarian Res. 2013 Sep 17;6(1):66.

- Enlace al texto completo (gratis o de pago) [1186/1757-2215-6-66](#)

AUTORES / AUTHORS: - Kalra RS; Bapat SA

RESUMEN / SUMMARY: - BACKGROUND: Earlier, proteomic profiling of a Serous Ovarian Carcinoma (SeOvCa) progression model in our lab had identified significantly enriched expression of three double-strand break (DSB) -repair proteins viz. RAD50, NPM1, and XRCC5 in transformed cells over pre-transformed, non-tumorigenic cells. Analysis of the functional relevance of enhanced levels of these proteins was explored in transformed ovarian cancer cells. METHODS: Expression profiling, validation and quantitation of the DSB-repair proteins at the transcriptional and protein levels were carried out. Further analyses included identification of their localization, distribution and modulation on exposure to Estradiol (E2) and cisplatin. Effects on silencing of each of these under conditions of genomic-stress were studied with respect to apoptosis, alterations in nuclear morphology and DNA fragmentation; besides profiling known mitotic and spindle check-point markers in DSB-repair. RESULTS: We identified that levels of these DSB-repair proteins were elevated not only in our model, but generally in cancer and are specifically triggered in response to genotoxic stress. Silencing of their expression led to aberrant DSB repair and consequently, p53/p21 mediated apoptosis. Further compromised functionality generated genomic instability. CONCLUSIONS: Present study elucidates a functional relevance of NPM1, RAD50 and XRCC5 DSB-repair proteins towards ensuring survival and evasion of apoptosis during ovarian transformation, emphasizing their contribution and association with disease progression in high-grade SeOvCa.

[875]

TÍTULO / TITLE: - Self-nanoemulsifying lipid carrier system for enhancement of oral bioavailability of etoposide by P-glycoprotein modulation: in vitro cell line and in vivo pharmacokinetic investigation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biomed Nanotechnol. 2013 Jul;9(7):1216-29.

AUTORES / AUTHORS: - Akhtar N; Talegaonkar S; Khar RK; Jaggi M

INSTITUCIÓN / INSTITUTION: - Faculty of Pharmacy, Formulation Research Laboratory, Department of Pharmaceutics, Hamdard University, New Delhi 110062, India.

RESUMEN / SUMMARY: - The purpose of this work is intended to investigate the potential of self-nanoemulsifying (SNE) drug delivery system for enhanced oral bioavailability of etoposide by P-glycoprotein (P-gp) modulation. The components of SNE formulation were optimized by their solubilization and emulsification efficiency. The ternary phase diagrams provided nanoemulsion existence ranges and the corresponding formulations were developed and evaluated via thermodynamic and dispersibility tests. The successful formulations were characterized for various parameters including time required for self-emulsification, percentage transmittance, droplet size, surface morphology, zeta potential and in vitro release. The etoposide loaded SNE9 formulation showed 2.6- and 11-fold higher permeability coefficient in apical to basolateral direction across Caco-2 monolayers as compared to the Etosid and plain drug solution, respectively. The etoposide loaded SNE9 formulation showed a higher cytotoxicity at the highest tested concentration compared to the blank SNE9 formulation and the free etoposide. Furthermore, an in vivo pharmacokinetic study of etoposide in SNE9 formulation showed 3.2- and 7.9-fold increase in relative oral bioavailability compared with that of etoposide in Etosid and drug suspension, respectively. Thus, the developed SNE drug delivery system could be a valuable tool for the effective oral delivery of etoposide.

[876]

TÍTULO / TITLE: - Growth Inhibition and Apoptosis-Inducing Effects of Cudraflavone B in Human Oral Cancer Cells via MAPK, NF-kappaB, and SIRT1 Signaling Pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Planta Med. 2013 Aug 14.

●● Enlace al texto completo (gratis o de pago) [1055/s-0033-1350778](https://doi.org/10.1055/s-0033-1350778)

AUTORES / AUTHORS: - Lee HJ; Auh QS; Lee YM; Kang SK; Chang SW; Lee DS; Kim YC; Kim EC

INSTITUCIÓN / INSTITUTION: - Department of Maxillofacial Tissue Regeneration and Research Center for Tooth & Periodontal Regeneration (MRC), School of Dentistry, Kyung Hee University, Seoul, Republic of Korea.

[877]

TÍTULO / TITLE: - Targeting mixed lineage kinases in ER-positive breast cancer cells leads to G2/M cell cycle arrest and apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncotarget. 2013 Aug;4(8):1158-71.

AUTORES / AUTHORS: - Wang L; Gallo KA; Conrad SE

INSTITUCIÓN / INSTITUTION: - Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI.

RESUMEN / SUMMARY: - Estrogen receptor (ER)-positive tumors represent the most common type of breast cancer, and ER-targeted therapies such as antiestrogens and aromatase inhibitors have therefore been widely used in breast cancer treatment. While many patients have benefited from these therapies, both innate and acquired resistance continue to be causes of treatment failure. Novel targeted therapeutics that could be used alone or in combination with endocrine agents to treat resistant tumors or to prevent their development are therefore needed. In this report, we examined the effects of inhibiting mixed-lineage kinase (MLK) activity on ER-positive breast cancer cells and non-tumorigenic mammary epithelial cells. Inhibition of MLK activity with the pan-MLK inhibitor CEP-1347 blocked cell cycle progression in G2 and early M phase, and induced apoptosis in three ER-positive breast cancer cell lines, including one with acquired antiestrogen resistance. In contrast, it had no effect on the cell cycle or apoptosis in two non-tumorigenic mammary epithelial cell lines. CEP-1347 treatment did not decrease the level of active ERK or p38 in any of the cell lines tested. However, it resulted in decreased JNK and NF-kappaB activity in the breast cancer cell lines. A JNK inhibitor mimicked the effects of CEP-1347 in breast cancer cells, and overexpression of c-Jun rescued CEP-1347-induced Bax expression. These results indicate that proliferation and survival of ER-positive breast cancer cells are highly dependent on MLK activity, and suggest that MLK inhibitors may have therapeutic efficacy for ER-positive breast tumors, including ones that are resistant to current endocrine therapies.

[878]

TÍTULO / TITLE: - Prognostic significance of ESR1 gene amplification, mRNA/protein expression and functional profiles in high-risk early breast cancer: a translational study of the Hellenic Cooperative Oncology Group (HeCOG).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e70634. doi:

10.1371/journal.pone.0070634. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0070634](#)

AUTORES / AUTHORS: - Pentheroudakis G; Kotoula V; Eleftheraki AG; Tsolaki E; Wirtz RM; Kalogeras KT; Batistatou A; Bobos M; Dimopoulos MA; Timotheadou E; Gogas H; Christodoulou C; Papadopoulou K; Efstratiou I; Scopa CD; Papaspyrou I; Vlachodimitropoulos D; Linardou H; Samantas E; Pectasides D; Pavlidis N; Fountzilas G

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Ioannina University Hospital, Ioannina, Greece. gpenther@otenet.gr

RESUMEN / SUMMARY: - BACKGROUND: Discrepant data have been published on the incidence and prognostic significance of ESR1 gene amplification in early breast cancer. PATIENTS AND METHODS: Formalin-fixed paraffin-embedded tumor blocks were collected from women with early breast cancer participating in two HeCOG adjuvant trials. Messenger RNA was studied by quantitative PCR, ER protein expression was centrally assessed using immunohistochemistry (IHC) and ESR1 gene copy number by dual fluorescent in situ hybridization probes. RESULTS: In a total of 1010 women with resected node-positive early breast adenocarcinoma, the tumoral ESR1/CEP6 gene ratio was suggestive of deletion in 159 (15.7%), gene gain in 551 (54.6%) and amplification in 42 cases (4.2%), with only 30 tumors (3%) harboring five or more ESR1 copies. Gene copy number ratio showed a significant, though weak correlation to mRNA and protein expression (Spearman's Rho <0.23, p = 0.01). ESR1 clusters were observed in 9.5% (57 gain, 38 amplification) of cases. In contrast to mRNA and protein expression, which were favorable prognosticators, gene copy number changes did not obtain prognostic significance. When ESR1/CEP6 gene ratio was combined with function (as defined by ER protein and mRNA expression) in a molecular classifier, the Gene Functional profile, it was functional status that impacted on prognosis. In univariate analysis, patients with functional tumors (positive ER protein expression and gene ratio normal or gain/amplification) fared better than those with non-functional tumors with ESR1 gain (HR for relapse or death 0.49-0.64, p = 0.003). Significant interactions were observed between gene gain/amplification and paclitaxel therapy (trend for DFS benefit from paclitaxel only in patients with ESR1 gain/amplification, p = 0.066) and Gene Functional profile with HER2 amplification (Gene Functional profile prognostic only in HER2-normal cases, p = 0.029). CONCLUSIONS: ESR1 gene deletion and amplification do not constitute per se prognostic markers, instead they can be classified to distinct prognostic groups according to their protein-mediated functional status.

[879]

TÍTULO / TITLE: - Paclitaxel loaded fibrinogen coated CdTe/ZnTe core shell nanoparticles for targeted imaging and drug delivery to breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biomed Nanotechnol. 2013 Oct;9(10):1657-71.

AUTORES / AUTHORS: - Rejinold NS; Baby T; Nair SV; Jayakumar R

INSTITUCIÓN / INSTITUTION: - Amrita Centre for Nanosciences and Molecular Medicine, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham University, Kochi 682041, India.

RESUMEN / SUMMARY: - The study aims at the targeted imaging using CdTe/ZnTe core shell QDs and delivery of paclitaxel (PTX) loaded fibrinogen coated yellow-QDs (PTX-

fib-yellow-QDs) towards breast cancer cells via the alpha5Beta1-integrins. We developed fibrinogen coated different sized CdTe/ZnTe core shell quantum dots of 2-10 nm size, which have been prepared by one-pot aqueous-phase approach. The fib-coated-QDs (fib-coated-QDs) and PTX-fib-yellow-QDs were prepared by two-step coacervation technique using CaCl₂ as cross-linker. Particle size of fib-coated-QDs was in between 60-220 nm while PTX-fib-yellow-QDs showed 180 +/- 40 nm. The MTT assay confirmed cytocompatibility of fib-coated-QDs on L929 and MCF-7 than bare QDs, whereas significant toxicity toward MCF-7 by PTX-fib-yellow-QDs was observed. The hemocompatible fib-coated-QDs showed enhanced localization and retention toward alpha5beta1-integrins +ve MCF-7 compared to alpha5beta1-integrins -ve L929 cells. The specific binding of fib-coated-yellow-QDs was further confirmed with alpha5beta1-integrins +ve HeLa and alpha5/beta1-integrins -ve HT29 cells. Cellular uptake studies revealed localization of PTX-fib-coated-yellow-QDs inside MCF-7 cells compared to the normal L929 cells. These results indicated that fib-coated-QDs could be used for targeted imaging and as a suitable "nanocarrier" aiming breast cancer cells.

[880]

TÍTULO / TITLE: - Apoptosis inhibitor showed a significant prognostic marker of relapsed oral cavity cancer after the curative resection surgery.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Med Assoc Thai. 2013 Aug;96(8):917-23.

AUTORES / AUTHORS: - Lausoonornsiri W; Chindavijak S; Sangariyanich E; Sakapiboonnan A

INSTITUCIÓN / INSTITUTION: - Clinical Research Center National Cancer Institute of Thailand, Bangkok, Thailand. wlausoon@yahoo.com

RESUMEN / SUMMARY: - BACKGROUND: Recurrence of oral cavity cancer after curative resection remains a major problem. Pathologic markers, which include positive margins, extracapsular nodal extension, lymphovascular invasion, and perineural invasion, predict likelihood of recurrence. However, there currently are no biomarkers that can be used to follow patients following the curative resection. Survivin, the anti-apoptotic protein is up-regulated in many types of cancer and is associated with poor prognosis and recurrence of cancer. We explored whether this biomarker predicted disease recurrence after curative resection of oral cancers. MATERIAL AND METHOD: Retrospective study of 47 patients with oral cancers who underwent curative surgery. Cases were assigned into two groups for analysis, with or without loco-regional recurrence/distant metastases. The study protocol was approved by the ethics committee of the National Cancer Institute. Biopsy sections both at tumor and margin were studied for expression of survivin and the tumor marker, CD44v6 by immunohistochemistry (IHC) technique. RESULTS: By using a scoring system, the surgical margin of the recurrent group showed a higher survivin score than

nonrecurrent group ($p = 0.003$). Interestingly, the primary tumor of the recurrent group showed a markedly higher survivin score than the non-recurrent group ($p < 0.001$). By contrast, the CD44v6 scores of the primary and the margins showed no significant difference between either group. CONCLUSION: The present study suggests that monitoring the survivin expression at the surgical margin may serve as a biomarker to evaluate the adequacy of the surgical margin and may serve to provide information to prepare a better preoperative plan for oral cancer surgery in order to improve the curative outcome.

[881]

TÍTULO / TITLE: - Gene Expression Profile of the A549 Human Non-Small Cell Lung Carcinoma Cell Line following Treatment with the Seeds of *Descurainia sophia*, a Potential Anticancer Drug.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:584604. doi: 10.1155/2013/584604. Epub 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1155/2013/584604](#)

AUTORES / AUTHORS: - Kim BY; Lee J; Park SJ; Bang OS; Kim NS

INSTITUCIÓN / INSTITUTION: - KM-Based Herbal Drug Research Group, Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon 305-811, Republic of Korea.

RESUMEN / SUMMARY: - *Descurainia sophia* has been traditionally used in Korean medicine for treatment of diverse diseases and their symptoms, such as cough, asthma, and edema. Our previous results showed that ethanol extract of the seeds of *D. sophia* (EEDS) has a potent cytotoxic effect on human cancer cells. In this study, we reveal the molecular events that are induced by EEDS treatment in A549 human lung cancer cells. The dose-dependent effect of EEDS on gene expression was measured via a microarray analysis. Gene ontology and pathway analyses were performed to identify functional involvement of genes regulated by EEDS. From gene expression analyses, two major dose-dependent patterns were observed after EEDS treatment. One pattern consisted of 1,680 downregulated genes primarily involved in metabolic processes ($FDR < 0.01$). The second pattern consisted of 1,673 upregulated genes primarily involved in signaling processes ($FDR < 0.01$). Pathway activity analyses revealed that the metabolism-related pathways and signaling-related pathways were regulated by the EEDS in dose-dependent and reciprocal manners. In conclusion, the identified biphasic regulatory mechanism involving activation of signaling pathways may provide molecular evidence to explain the inhibitory effect of EEDS on A549 cell growth.

[882]

TÍTULO / TITLE: - Ex vivo programming of dendritic cells by mitochondria-targeted nanoparticles to produce interferon-gamma for cancer immunotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ACS Nano. 2013 Aug 27;7(8):7392-402. doi: 10.1021/nn403158n. Epub 2013 Aug 6.

●● Enlace al texto completo (gratis o de pago) [1021/nn403158n](#)

AUTORES / AUTHORS: - Marrache S; Tundup S; Harn DA; Dhar S

INSTITUCIÓN / INSTITUTION: - NanoTherapeutics Research Laboratory, Department of Chemistry, and double daggerDepartment of Physiology and Pharmacology, University of Georgia, Athens, Georgia 30602, United States.

RESUMEN / SUMMARY: - One of the limitations for clinical applications of dendritic cell (DC)-based cancer immunotherapy is the low potency in generating tumor antigen specific T cell responses. We examined the immunotherapeutic potential of a mitochondria-targeted nanoparticle (NP) based on a biodegradable polymer and zinc phthalocyanine (ZnPc) photosensitizer (T-ZnPc-NPs). Here, we report that tumor antigens generated from treatment of breast cancer cells with T-ZnPc-NPs upon light stimulation activate DCs to produce high levels of interferon-gamma, an important cytokine considered as a product of T and natural killer cells. The remarkable ex vivo DC stimulation ability of this tumor cell supernatant is a result of an interleukin (IL)-12/IL-18 autocrine effect. These findings contribute to the understanding of how in situ light activation amplifies the host immune responses when NPs deliver the photosensitizer to the mitochondria and open up the possibility of using mitochondria-targeted-NP-treated, light-activated cancer cell supernatants as possible vaccines.

[883]

TÍTULO / TITLE: - Proliferation inhibition and apoptosis induction of imatinib-resistant chronic myeloid leukemia cells via PPP2R5C down-regulation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Hematol Oncol. 2013 Sep 3;6(1):64.

●● Enlace al texto completo (gratis o de pago) [1186/1756-8722-6-64](#)

AUTORES / AUTHORS: - Shen Q; Liu S; Chen Y; Yang L; Chen S; Wu X; Li B; Lu Y; Zhu K; Li Y

RESUMEN / SUMMARY: - Despite the success of imatinib and other tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) remains largely incurable, and a number of CML patients die due to Abl mutation-related drug resistance and blast crisis. The aim of this study was to evaluate proliferation inhibition and apoptosis induction by down-regulating PPP2R5C gene expression in the imatinib-sensitive and imatinib-resistant CML cell lines K562, K562R (imatinib resistant without an Abl gene mutation), 32D-Bcr-Abl WT (imatinib-sensitive murine CML cell line with a wild type abl gene) and 32D-Bcr-Abl T315I (imatinib resistant with a T315I Abl gene mutation) and primary cells from CML patients by RNA interference. PPP2R5C siRNAs numbered 799 and 991 were obtained by chemosynthesis. Non-silencing siRNA scrambled

control (SC)-treated, mock-transfected, and untreated cells were used as controls. The PPP2R5C mRNA and protein expression levels in treated CML cells were analyzed by quantitative real-time PCR and Western blotting, and in vitro cell proliferation was assayed with the cell counting kit-8 method. The morphology and percentage of apoptosis were revealed by Hoechst 33258 staining and flow cytometry (FCM). The results demonstrated that both siRNAs had the best silencing results after nucleofection in all four cell lines and primary cells. A reduction in PPP2R5C mRNA and protein levels was observed in the treated cells. The proliferation rate of the PPP2R5C-siRNA-treated CML cell lines was significantly decreased at 72 h, and apoptosis was significantly increased. Significantly higher proliferation inhibition and apoptosis induction were found in K562R cells treated with PPP2R5C-siRNA799 than K562 cells. In conclusion, the suppression of PPP2R5C by RNA interference could inhibit proliferation and effectively induce apoptosis in CML cells that were either imatinib sensitive or resistant. Down-regulating PPP2R5C gene expression might be considered as a new therapeutic target strategy for CML, particularly for imatinib-resistant CML.

[884]

TÍTULO / TITLE: - Gemcitabine-mediated tumour regression and p53-dependent gene expression: implications for colon and pancreatic cancer therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 5;4:e791. doi: 10.1038/cddis.2013.307.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.307](#)

AUTORES / AUTHORS: - Hill R; Rabb M; Madureira PA; Clements D; Gujar SA; Waisman DM; Giacomantonio CA; Lee PW

INSTITUCIÓN / INSTITUTION: - [1] Centre for Molecular and Structural Biomedicine, University of Algarve, Algarve, Portugal [2] Department of Microbiology & Immunology, Dalhousie University, Halifax, Nova Scotia, Canada [3] Department of Medicine, University of Algarve, Algarve, Portugal.

RESUMEN / SUMMARY: - Gemcitabine is a chemotherapeutic that is widely used for the treatment of a variety of haematological malignancies and has become the standard chemotherapy for the treatment of advanced pancreatic cancer. Combinational gemcitabine regimes (e.g. with doxorubicin) are being tested in clinical trials to treat a variety of cancers, including colon cancer. The limited success of these trials has prompted us to pursue a better understanding of gemcitabine's mechanism of cell killing, which could dramatically improve the therapeutic potential of this agent. For comparison, we included gamma irradiation that triggers robust cell cycle arrest and Cr(VI), which is a highly toxic chemical that induces a robust p53-dependent apoptotic response. Gemcitabine induced a potent p53-dependent apoptosis that correlated with the accumulation of pro-apoptotic proteins such as PUMA and Bax. This is accompanied by a drastic reduction in p21 and 14-3-3sigma protein levels, thereby significantly sensitizing the cells to apoptosis. In vitro and in vivo studies demonstrated

that gemcitabine required PUMA transcription to instigate an apoptotic programme. This was in contrast to Cr(VI)-induced apoptosis that required Bax and was independent of transcription. An examination of clinical colon and pancreatic cancer tissues shows higher p53, p21, 14-3-3sigma and Bax expression compared with matched normal tissues, yet there is a near absence of PUMA protein. This may explain why gemcitabine shows only limited efficacy in the treatment of these cancers. Our results raise the possibility that targeting the Bax-dependent cell death pathway, rather than the PUMA pathway, could result in significantly improved patient outcome and prognosis for these cancers.

[885]

TÍTULO / TITLE: - Chlorogenic acid induced apoptosis and inhibition of proliferation in human acute promyelocytic leukemia HL60 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Oct;8(4):1106-10. doi: 10.3892/mmr.2013.1652. Epub 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1652](#)

AUTORES / AUTHORS: - Liu YJ; Zhou CY; Qiu CH; Lu XM; Wang YT

INSTITUCIÓN / INSTITUTION: - College of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, P.R. China.

RESUMEN / SUMMARY: - Chlorogenic acid (CA), is found in high abundance in the leaves of a number of plants and has antibacterial, antiphlogistic, antimutagenic, antioxidant and other biological activities. It reportedly possesses antitumor activity via the induction of apoptosis in chronic myelogenous leukemia (CML) cell lines, including U937 and K562 cells. However, the effects of CA on human acute promyelocytic leukemia (APL) HL60 cells remains unknown. In the current study, the ability of CA to cause G0/G1 cycle arrest and induce apoptosis in the treatment of human APL HL60 cells was investigated. Following 5 days treatment with 1, 5 and 10 microM CA, cell viability and the effects of CA on the growth of HL60 cells were investigated using a growth curve constructed using trypan blue staining. Induction of apoptosis and inhibition of cell proliferation were estimated using Wright'sGiemsa staining, Hoechst 33342 and propidium iodide (PI) staining, DNA ladder analysis and flow cytometry, following 48 h cell treatment with various doses of CA. The results indicated that the growth of HL60 cells reached a plateau phase at 72 h and the proliferation inhibition rate of HL60 cells in CA treated groups was significantly higher compared with the control, in a time and dosedependent manner. However, the level of apoptosis of HL60 cells treated with CA markedly increased and formed more apoptotic bodies compared with the cells with no drug treatment, according to the Wright'sGiemsa staining, Hoechst 33342 and PI staining, respectively. Using DNA ladder analysis and flow cytometry it was shown that a significant characteristic DNA ladder was observed when treated with CA. CA was capable of arresting cell cycle at G0/G1 phase.

Apoptosis of HL60 cells treated with CA for 48 h was promoted significantly in a dosedependent manner, as well as the inhibition of proliferation. The observations revealed that CA inhibits proliferation and induces preprophase apoptosis of HL60 cells. Thus, the concentration of 10 microM may be the optimal dose for treatment human acute promyelocytic leukemia.

[886]

TÍTULO / TITLE: - The anti-tumor drug bleomycin preferentially cleaves at the transcription start sites of actively transcribed genes in human cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Mol Life Sci. 2013 Aug 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00018-013-1456-4](https://doi.org/10.1007/s00018-013-1456-4)

AUTORES / AUTHORS: - Murray V; Chen JK; Galea AM

INSTITUCIÓN / INSTITUTION: - School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW, 2052, Australia, v.murray@unsw.edu.au.

RESUMEN / SUMMARY: - The genome-wide pattern of DNA cleavage at transcription start sites (TSSs) for the anti-tumor drug bleomycin was examined in human HeLa cells using next-generation DNA sequencing. It was found that actively transcribed genes were preferentially cleaved compared with non-transcribed genes. The 143,600 identified human TSSs were split into non-transcribed genes (82,596) and transcribed genes (61,004) for HeLa cells. These transcribed genes were further split into quintiles of 12,201 genes comprising the top 20, 20-40, 40-60, 60-80, and 80-100 % of expressed genes. The bleomycin cleavage pattern at highly transcribed gene TSSs was greatly enhanced compared with purified DNA and non-transcribed gene TSSs. The top 20 and 20-40 % quintiles had a very similar enhanced cleavage pattern, the 40-60 % quintile was intermediate, while the 60-80 and 80-100 % quintiles were close to the non-transcribed and purified DNA profiles. The pattern of bleomycin enhanced cleavage had peaks that were approximately 200 bp apart, and this indicated that bleomycin was identifying the presence of phased nucleosomes at TSSs. Hence bleomycin can be utilized to detect chromatin structures that are present at actively transcribed genes. In this study, for the first time, the pattern of DNA damage by a clinically utilized cancer chemotherapeutic agent was performed on a human genome-wide scale at the nucleotide level.

[887]

TÍTULO / TITLE: - Propyl-2-(8-(3,4-difluorobenzyl)-2',5'-dioxo-8-azaspiro[bicyclo[3.2.1]octane-3,4'-imidazolidine]-1'-yl) acetate induces apoptosis in human leukemia cells through mitochondrial pathway following cell cycle arrest.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 26;8(7):e69103. doi: 10.1371/journal.pone.0069103. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069103](https://doi.org/10.1371/journal.pone.0069103)

AUTORES / AUTHORS: - Kavitha CV; Nambiar M; Narayanaswamy PB; Thomas E; Rathore U; Ananda Kumar CS; Choudhary B; Rangappa KS; Raghavan SC

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Indian Institute of Science, Bangalore, Karnataka, India.

RESUMEN / SUMMARY: - **BACKGROUND:** Due to the functional defects in apoptosis signaling molecules or deficient activation of apoptosis pathways, leukemia has become an aggressive disease with poor prognosis. Although the majority of leukemia patients initially respond to chemotherapy, relapse is still the leading cause of death. Hence targeting apoptosis pathway would be a promising strategy for the improved treatment of leukemia. Hydantoin derivatives possess a wide range of important biological and pharmacological properties including anticancer properties. Here we investigated the antileukemic activity and mechanism of action of one of the potent azaspiro hydantoin derivative, (ASHD). **MATERIALS AND METHODS:** To investigate the antileukemic efficacy of ASHD, we have used MTT assay, cell cycle analysis by FACS, tritiated thymidine incorporation assay, Annexin V staining, JC1 staining and western blot analysis. **RESULTS:** Results showed that ASHD was approximately 3-fold more potent than the parent compounds in inducing cytotoxicity. Tritiated thymidine assay in conjunction with cell cycle analysis suggests that ASHD inhibited the growth of leukemic cells. The limited effect of ASHD on cell viability of normal cells indicated that it may be specifically directed to cancer cells. Translocation of phosphatidyl serine, activation of caspase 3, caspase 9, PARP, alteration in the ratio of BCL2/BAD protein expression as well as the loss of mitochondrial membrane potential suggests activation of the intrinsic pathway of apoptosis. **CONCLUSION:** These results could facilitate the future development of novel hydantoin derivatives as chemotherapeutic agents for leukemia.

[888]

TÍTULO / TITLE: - Inhibition of ubiquitin conjugating enzyme UBE2C reduces proliferation and sensitizes breast cancer cells to radiation, doxorubicin, tamoxifen and letrozole.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Oncol (Dordr). 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1007/s13402-013-0150-8](https://doi.org/10.1007/s13402-013-0150-8)

AUTORES / AUTHORS: - Rawat A; Gopal G; Selvaluxmy G; Rajkumar T

INSTITUCIÓN / INSTITUTION: - Department of Molecular Oncology, Cancer Institute (WIA), 38, Sardar Patel Road, Chennai, 600036, India.

RESUMEN / SUMMARY: - **PURPOSE:** The objective of this study was to determine radiation, doxorubicin, tamoxifen and letrozole sensitivity of breast cancer cells in response to functional inhibition of the ubiquitin conjugating enzyme UBE2C.

METHODS: Taqman Real time PCR was performed to measure UBE2C levels in breast cancer cell lines and control HBL100 and HEK293T cells. A dominant negative form of UBE2C (DN-UBE2C) was used to functionally inhibit wild type UBE2C. Cell proliferation and anchorage independent growth were measured by colorimetric and soft agar assays, respectively. Radiation, doxorubicin, tamoxifen and letrozole responses of the cell lines were assessed by colorimetric and clonogenic assays. **RESULTS:** Overexpression of UBE2C was observed in all breast cancer cell lines tested using quantitative real time PCR. UBE2C expression was found to be highest in MDAMB231 and relatively lowest in MCF7 cells, compared to control cells. Both the growth rate and the anchorage independent growth of MCF7 and MDAMB231 cells transfected with DN-UBE2C were significantly reduced compared to cells transfected with vector alone. MCF7 and MDAMB231 cells expressing DN-UBE2C were significantly more sensitive to different doses of radiation and doxorubicin compared to both wild type and vector alone transfected cells. In addition, DN-UBE2C transfected MCF7 cells were more sensitive to inhibition by tamoxifen and letrozole compared to wild type and vector alone transfected cells. **CONCLUSIONS:** Our results show that inhibition of UBE2C sensitizes breast cancer cells to radiation, doxorubicin and hormone blocking agents. UBE2C may, therefore, serve as a potential therapeutic target aimed at inducing radiation and chemo sensitization.

[889]

TÍTULO / TITLE: - A ginseng metabolite, compound K, induces autophagy and apoptosis via generation of reactive oxygen species and activation of JNK in human colon cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 1;4:e750. doi: 10.1038/cddis.2013.273.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cddis.2013.273](#)

AUTORES / AUTHORS: - Kim AD; Kang KA; Kim HS; Kim DH; Choi YH; Lee SJ; Kim HS; Hyun JW

INSTITUCIÓN / INSTITUTION: - School of Medicine and Institute for Nuclear Science and Technology, Jeju National University, Jeju, Korea.

RESUMEN / SUMMARY: - Compound K (20-O-(beta-D-glucopyranosyl)-20(S)-protopanaxadiol) is an active metabolite of ginsenosides and induces apoptosis in various types of cancer cells. This study investigated the role of autophagy in compound K-induced cell death of human HCT-116 colon cancer cells. Compound K activated an autophagy pathway characterized by the accumulation of vesicles, the increased positive acridine orange-stained cells, the accumulation of LC3-II, and the elevation of autophagic flux. Whereas blockade of compound K-induced autophagy by 3-methyladenine and bafilomycin A1 significantly increased cell viability. In addition, compound K augmented the time-dependent expression of the autophagy-related proteins Atg5, Atg6, and Atg7. However, knockdown of Atg5, Atg6, and Atg7 markedly

inhibited the detrimental impact of compound K on LC3-II accumulation and cell vitality. Compound K-provoked autophagy was also linked to the generation of intracellular reactive oxygen species (ROS); both of these processes were mitigated by the pre-treatment of cells with the antioxidant N-acetylcysteine. Moreover, compound K activated the c-Jun NH2-terminal kinase (JNK) signaling pathway, whereas downregulation of JNK by its specific inhibitor SP600125 or by small interfering RNA against JNK attenuated autophagy-mediated cell death in response to compound K. Compound K also provoked apoptosis, as evidenced by an increased number of apoptotic bodies and sub-G1 hypodiploid cells, enhanced activation of caspase-3 and caspase-9, and modulation of Bcl-2 and Bcl-2-associated X protein expression. Notably, compound K-stimulated autophagy as well as apoptosis was induced by disrupting the interaction between Atg6 and Bcl-2. Taken together, these results indicate that the induction of autophagy and apoptosis by compound K is mediated through ROS generation and JNK activation in human colon cancer cells.

[890]

TÍTULO / TITLE: - Staphylococcal enterotoxins of the enterotoxin gene cluster (egcSEs) induce nitrous oxide- and cytokine dependent tumor cell apoptosis in a broad panel of human tumor cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Cell Infect Microbiol. 2013;3:38. doi: 10.3389/fcimb.2013.00038.

●● [Enlace al texto completo \(gratis o de pago\) 3389/fcimb.2013.00038](#)

AUTORES / AUTHORS: - Terman DS; Serier A; Dauwalder O; Badiou C; Dutour A; Thomas D; Brun V; Bienvenu J; Etienne J; Vandenesch F; Lina G

INSTITUCIÓN / INSTITUTION: - Molecular Genetics Program, Jenomic Research Institute, Carmel, CA 93953 , USA. dst@sbcglobal.net

RESUMEN / SUMMARY: - The egcSEs comprise five genetically linked staphylococcal enterotoxins, SEG, SEI, SEIM, SEIN, and SEIO and two pseudotoxins which constitute an operon present in up to 80% of Staphylococcus aureus isolates. A preparation containing these proteins was recently used to treat advanced lung cancer with pleural effusion. We investigated the hypothesis that egcSEs induce nitrous oxide (NO) and associated cytokine production and that these agents may be involved in tumoricidal effects against a broad panel of clinically relevant human tumor cells. Preliminary studies showed that egcSEs and SEA activated T cells (range: 11-25%) in a concentration dependent manner. Peripheral blood mononuclear cells (PBMCs) stimulated with equimolar quantities of egcSEs expressed NO synthase and generated robust levels of nitrite (range: 200-250 μ M), a breakdown product of NO; this reaction was inhibited by NG-monomethyl-L-arginine (L-NMMA) (0.3 mM), an NO synthase antagonist. Cell free supernatants (CSFs) of all egcSE-stimulated PBMCs were also equally effective in inducing concentration dependent tumor cell apoptosis in a

broad panel of human tumor cells. The latter effect was due in part to the generation of NO and TNF-alpha since it was significantly abolished by L-NMMA, anti-TNF-alpha antibodies, respectively, and a combination thereof. A hierarchy of tumor cell sensitivity to these CFSs was as follows: lung carcinoma > osteogenic sarcoma > melanoma > breast carcinoma > neuroblastoma. Notably, SEG induced robust activation of NO/TNFalpha-dependent tumor cell apoptosis comparable to the other egcSEs and SEA despite TNF-alpha and IFN-gamma levels that were 2 and 8 fold lower, respectively, than the other egcSEs and SEA. Thus, egcSEs produced by *S. aureus* induce NO synthase and the increased NO formation together with TNF-alpha appear to contribute to egcSE-mediated apoptosis against a broad panel of human tumor cells.

[891]

TÍTULO / TITLE: - Induction of mitochondrial dependent apoptosis and cell cycle arrest in human promyelocytic leukemia HL-60 cells by an extract from *Dorstenia psilurus*: a spice from Cameroon.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Sep 10;13(1):223.

●● Enlace al texto completo (gratis o de pago) [1186/1472-6882-13-223](#)

AUTORES / AUTHORS: - Pieme CA; Guru SK; Pantaleon A; Kumar S; Bathelemy N; Jeanne NY; Bhushan S; Saxena AK

RESUMEN / SUMMARY: - BACKGROUND: The use of edible plants is an integral part of dietary behavior in the West region of Cameroon. *Dorstenia psilurus* (Moraceae) is widely used as spice and as medicinal plant for the treatment of several diseases in Cameroon. The aim of this study is to investigate the cytotoxic and apoptotic potential of methanol extract of *D. psilurus* in human promyelocytic leukemia (HL-60) cells and prostate cancer (PC-3) cells. METHODS: Cytotoxicity of *D. psilurus* extract was tested in HL-60 and PC-3 cells using 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay and flow cytometric methods RESULTS: The methanol extract of *D. psilurus* have significant in vitro cytotoxic activity in HL-60 cells and PC-3 cells with IC50 value of 12 +/-1.54 mug/ml and 18 +/- 0.45 mug/ml respectively after 48 h. The mechanism of antiproliferative activity showed that after 24 h, *D. psilurus* extract induces apoptosis on HL-60 cells by the generation of reactive oxygen species (ROS) along with concurrent loss of mitochondrial membrane potential, modification in the DNA distribution and enhance of G2/M phase cell cycle. CONCLUSION: The extract induces apoptosis of HL-60 cells associated with ROS production, loss of mitochondrial membrane potential and apoptotic DNA fragmentation.

[892]

TÍTULO / TITLE: - The effect of aqueous cinnamon extract on the apoptotic process in acute myeloid leukemia HL-60 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Adv Biomed Res. 2013 Mar 6;2:25. doi: 10.4103/2277-9175.108001.

●● Enlace al texto completo (gratis o de pago) [4103/2277-9175.108001](#)

AUTORES / AUTHORS: - Assadollahi V; Parivar K; Roudbari NH; Khalatbary AR; Motamedi M; Ezatpour B; Dashti GR

INSTITUCIÓN / INSTITUTION: - Razi Herbal Medicines Research Center, Lorestan University of Medical sciences, Khorramabad, Iran.

RESUMEN / SUMMARY: - BACKGROUND: Acute promyelocytic leukemia (APL) is an acute leukemia diagnosed by translocation of chromosomes 15 and 17 [T (15,17)] and aggregation of neoplastic promyelocytes which are incapable of being converted into mature cells. Today, many tend to use medicinal herbs in studies and clinical applications for treatment of cancers. Cinnamon with scientific name "cinnamomumzelanicum" is a shrub of Laurales order, lauraceae family with cinnamomum genus. It is a medicinal shrub with anti-proliferation effect on tumor cells. This study was conducted to determine the effects of aqueous cinnamon extract on HL-60 cells as a model for APL. MATERIALS AND METHODS: In this in vitro experimental study, HL-60 cell line was cultured under the influence of cinnamon extract's concentrations of 0.01, 0.1, 1, and 2 mg/ml in with intervals of 24, 48, and 72 h. Growth inhibition and toxic effects of cinnamon extract were evaluated through tetrazolium salt reduction. The effect of this herb on the cell cycle was studied by flow cytometry. The Hoechst stain was used to detect apoptotic cell nuclei. RESULTS: Cinnamon extract inhibited the growth of HL-60 cells as correlated with concentration and time. After 72 h of treating HL-60 cells with 0.01 mg/l cinnamon extract, the growth of cells was inhibited by 90.1%. Cinnamon extract stopped the cell cycle in G1 phase and the Hoechst staining verified the apoptotic process in those cells. CONCLUSION: Considering the inhibitory property of cinnamon extract, we recommend it as a single drug or besides other medications for treating promyelocytic leukemia.

[893]

TÍTULO / TITLE: - Autophagy-Dependent Survival of Mutant B-Raf Melanoma Cells Selected for Resistance to Apoptosis Induced by Inhibitors against Oncogenic B-Raf.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomol Ther (Seoul). 2013 Mar;21(2):114-20. doi: 10.4062/biomolther.2013.012.

●● Enlace al texto completo (gratis o de pago) [4062/biomolther.2013.012](#)

AUTORES / AUTHORS: - Ahn JH; Lee M

INSTITUCIÓN / INSTITUTION: - Division of Life Sciences, College of Life Sciences and Bioengineering, University of Incheon, Incheon 406-772, Republic of Korea.

RESUMEN / SUMMARY: - Most patients with mutant B-Raf melanomas respond to inhibitors of oncogenic B-Raf but resistance eventually emerges. To better understand the mechanisms that determine the long-term responses of mutant B-Raf melanoma cells to B-Raf inhibitor, we used chronic selection to establish B-Raf (V600E) melanoma clones with acquired resistance to the new oncogenic B-Raf inhibitor UI-152. Whereas the parental A375P cells were highly sensitive to UI-152 (IC₅₀<0.5 μM), the resistant sub-line (A375P/Mdr) displayed strong resistance to UI-152 (IC₅₀>20 μM). Immunofluorescence analysis indicated the absence of an increase in the levels of P-glycoprotein multidrug resistance (MDR) transporter in A375P/Mdr cells, suggesting that resistance was not attributable to P-glycoprotein overexpression. In UI-152-sensitive A375P cells, the anti-proliferative activity of UI-152 appeared to be due to cell-cycle arrest at G₀/G₁ with the induction of apoptosis. However, we found that A375P/Mdr cells were resistant to the apoptosis induced by UI-152. Interestingly, UI-152 preferentially induced autophagy in A375P/Mdr cells but not in A375P cells, as determined by GFP-LC3 puncta/cell counts. Further, autophagy inhibition with 3-methyladenine (3-MA) partially augmented growth inhibition of A375P/Mdr cells by UI-152, which implies that a high level of autophagy may protect UI-152-treated cells from undergoing growth inhibition. Together, our data implicate high rates of autophagy as a key mechanism of acquired resistance to the oncogenic B-Raf inhibitor, in support of clinical studies in which combination therapy with autophagy targeted drugs is being designed to overcome resistance.

[894]

TÍTULO / TITLE: - Alpha cyano-4-hydroxy-3-methoxycinnamic Acid inhibits proliferation and induces apoptosis in human breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 5;8(9):e72953. doi: 10.1371/journal.pone.0072953.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072953](https://doi.org/10.1371/journal.pone.0072953)

AUTORES / AUTHORS: - Hamdan L; Arrar Z; Al Muataz Y; Suleiman L; Negrier C; Mulengi JK; Boukerche H

INSTITUCIÓN / INSTITUTION: - Unite de Recherche Mixte EA4174, Universite Claude Bernard Lyon1, INSERM, Lyon, France ; Department de Chimie Organique, Substances Naturelles et Analyses, University de Tlemcen, Tlemcen, Algerie.

RESUMEN / SUMMARY: - This study investigated the underlying mechanism of 4-hydroxy-3-methoxycinnamic acid (ACCA), on the growth of breast cancer cells and normal immortal epithelial cells, and compared their cytotoxic effects responses. Treatment of breast cancer cells (MCF-7, T47D, and MDA-231) with ACCA resulted in dose- and time-dependent decrease of cell proliferation, viability in colony formation assay, and programmed cell death (apoptosis) with minimal effects on non-tumoral cells. The ability of ACCA to suppress growth in cancer cells not expressing or containing defects

in p53 gene indicates a lack of involvement of this critical tumor suppressor element in mediating ACCA-induced growth inhibition. Induction of apoptosis correlated with an increase in Bax protein, an established inducer of programmed cell death, and the ratio of Bax to Bcl-2, an established inhibitor of apoptosis. We also documented the ability of ACCA to inhibit the migration and invasion of MDA-231 cells with ACCA in vitro. Additionally, tumor growth of MDA-231 breast cancer cells in vivo was dramatically affected with ACCA. On the basis of its selective anticancer inhibitory activity on tumor cells, ACCA may represent a promising therapeutic drug that should be further evaluated as a chemotherapeutic agent for human breast cancer.

[895]

TÍTULO / TITLE: - The Role of Fcγ Receptor Polymorphisms in the Response to Anti-Tumor Necrosis Factor Therapy in Psoriasis: A Pharmacogenetic Study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - JAMA. 2013 Jul 31. doi: 10.1001/jamadermatol.2013.4632. ●●

JAMA: <> Dermatol. 2013 Jul 31. doi: 10.1001/jamadermatol.2013.4632.

●● [Enlace al texto completo \(gratis o de pago\)](#)

1001/jamadermatol.2013.4632

AUTORES / AUTHORS: - Julia M; Guilabert A; Lozano F; Suarez-Casasus B; Moreno N; Carrascosa JM; Ferrandiz C; Pedrosa E; Alsina-Gibert M; Mascaro JM

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, Hospital Clinic de Barcelona, Barcelona, España.

RESUMEN / SUMMARY: - IMPORTANCE Variability in genes encoding proteins involved in the immunological pathways of biological therapy may account for the differences observed in outcomes of anti-tumor necrosis factor (TNF) treatment of psoriasis.

OBJECTIVE To assess the role of 2 Fcγ receptor (FcγR) polymorphisms in the response to anti-TNF therapy in psoriasis. **DESIGN** Retrospective series of patients with psoriasis who received anti-TNF therapy (infliximab, adalimumab, or etanercept) from January 1, 2007, through December 31, 2010. Patients were followed up for 12 weeks. **SETTING** Two psoriasis referral centers. **PARTICIPANTS** Seventy treatment-naive patients with moderate to severe psoriasis who received anti-TNF agents.

INTERVENTION Patients underwent FcγRIIA-H131R and FcγRIIIA-V158F polymorphism genotyping. **MAIN OUTCOMES AND MEASURES** The Psoriasis Area and Severity Index and the body surface area were assessed at baseline and at treatment weeks 6 to 8 and 12. The polymorphism genotypes were correlated with the treatment outcomes. **RESULTS** Bivariate analysis showed a nonsignificant association between FcγR low-affinity genotypes and greater improvement in the Psoriasis Area and Severity Index and body surface area at the end of treatment. Conversely, patients harboring high-affinity alleles presented a greater reduction in body surface area at the intermediate point, which remained independent in the multivariate analysis. We also detected an additive effect of both polymorphisms in the multivariate analysis. High-

affinity alleles may contribute to a quicker response owing to a more efficient removal of relevant cells expressing TNF. CONCLUSIONS AND RELEVANCE Preliminary results of this pilot study on the pharmacogenetics of FcgammaR and biological therapy in psoriasis suggest a role with clinical implications for FcgammaRIIA-H131R and FcgammaRIIIA-V158F polymorphisms in the outcome of anti-TNF treatment of psoriasis. These results might help dermatologists in guiding therapeutic decisions, especially in very severe cases where a quick response is needed.

[896]

TÍTULO / TITLE: - EGFR inhibitors exacerbate differentiation and cell cycle arrest induced by retinoic acid and vitamin D 3 in acute myeloid leukemia cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Cycle. 2013 Sep 15;12(18):2978-91. doi: 10.4161/cc.26016. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [4161/cc.26016](#)

AUTORES / AUTHORS: - Lainey E; Wolfromm A; Sukkurwala AQ; Micol JB; Fenaux P; Galluzzi L; Kepp O; Kroemer G

INSTITUCIÓN / INSTITUTION: - INSERM; U848; Villejuif, France; Gustave Roussy; Villejuif, France; Universite Paris Sud/Paris XI; Le Kremlin Bicetre, France; Hopital Robert Debre; AP-HP; Paris, France.

RESUMEN / SUMMARY: - By means of an unbiased, automated fluorescence microscopy-based screen, we identified the epidermal growth factor receptor (EGFR) inhibitors erlotinib and gefitinib as potent enhancers of the differentiation of HL-60 acute myeloid leukemia (AML) cells exposed to suboptimal concentrations of vitamin A (all-trans retinoic acid, ATRA) or vitamin D (1alpha,25-hydroxycholecalciferol, VD). Erlotinib and gefitinib alone did not promote differentiation, yet stimulated the acquisition of morphological and biochemical maturation markers (including the expression of CD11b and CD14 as well as increased NADPH oxidase activity) when combined with either ATRA or VD. Moreover, the combination of erlotinib and ATRA or VD synergistically induced all the processes that are normally linked to terminal hematopoietic differentiation, namely, a delayed proliferation arrest in the G₀/G₁ phase of the cell cycle, cellular senescence, and apoptosis. Erlotinib potently inhibited the (auto)phosphorylation of mitogen-activated protein kinase 14 (MAPK14, best known as p38(MAPK)) and SRC family kinases (SFKs). If combined with the administration of ATRA or VD, the inhibition of p38(MAPK) or SFKs with specific pharmacological agents mimicked the pro-differentiation activity of erlotinib. These data were obtained with 2 distinct AML cell lines (HL-60 and MOLM-13 cells) and could be confirmed on primary leukemic blasts isolated from the circulation of AML patients. Altogether, these findings point to a new regimen for the treatment of AML, in which naturally occurring pro-differentiation agents (ATRA or VD) may be combined with EGFR inhibitors.

[897]

TÍTULO / TITLE: - Samsoeum, a traditional herbal medicine, elicits apoptotic and autophagic cell death by inhibiting Akt/mTOR and activating the JNK pathway in cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Sep 23;13(1):233.

●● Enlace al texto completo (gratis o de pago) [1186/1472-6882-13-233](#)

AUTORES / AUTHORS: - Kim A; Yim NH; Ma JY

RESUMEN / SUMMARY: - BACKGROUND: Samsoeum (SSE), a traditional herbal formula, has been widely used to treat cough, fever, congestion, and emesis for centuries. Recent studies have demonstrated that SSE retains potent pharmacological efficiency in anti-allergic and anti-inflammatory reactions. However, the anti-cancer activity of SSE and its underlying mechanisms have not been studied. Thus, the present study was designed to determine the effect of SSE on cell death and elucidate its detailed mechanism. METHODS: Following SSE treatment, cell growth and cell death were measured using an MTT assay and trypan blue exclusion assay, respectively. Cell cycle arrest and YO-PRO-1 uptake were assayed using flow cytometry, and LC3 redistribution was observed using confocal microscope. The mechanisms of anti-cancer effect of SSE were investigated through western blot analysis. RESULTS: We initially found that SSE caused dose- and time-dependent cell death in cancer cells but not in normal primary hepatocytes. In addition, during early SSE treatment (6--12 h), cells were arrested in G2/M phase concomitant with up-regulation of p21 and p27 and down-regulation of cyclin D1 and cyclin B1, followed by an increase in apoptotic YO-PRO-1 (+) cells. SSE also induced autophagy via up-regulation of Beclin-1 expression, conversion of microtubule-associated protein light chain 3 (LC3) I to LC3-II, and re-distribution of LC3, indicating autophagosome formation. Moreover, the level of B-cell lymphoma 2 (Bcl-2), which is critical for cross-talk between apoptosis and autophagy, was significantly reduced in SSE-treated cells. Phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) was increased, followed by suppression of the protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway, and phosphorylation of mitogen-activated protein kinases (MAPKs) in response to SSE treatment. In particular, among MAPKs inhibitors, only the c-Jun N-terminal kinase (JNK)-specific inhibitor SP600125 nearly blocked SSE-induced increases in Beclin-1, LC3-II, and Bax expression and decreases in Bcl-2 expression, indicating that JNK activation plays critical role in cell death caused by SSE. CONCLUSIONS: These findings suggest that SSE efficiently induces cancer cell death via apoptosis as well as autophagy through modification of the Akt/mTOR and JNK signaling pathways. SSE may be as a potent traditional herbal medicine for treating malignancies.

[898]

TÍTULO / TITLE: - Bcl-6 expression and lactate dehydrogenase level predict prognosis of primary gastric diffuse large B-cell lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Formos Med Assoc. 2013 Jul;112(7):382-9. doi: 10.1016/j.jfma.2012.07.031. Epub 2012 Oct 11.

●● Enlace al texto completo (gratis o de pago) [1016/j.jfma.2012.07.031](http://dx.doi.org/10.1016/j.jfma.2012.07.031)

AUTORES / AUTHORS: - Chung KM; Chang ST; Huang WT; Lu CL; Wu HC; Hwang WS; Chang KY; Chuang SS

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND/PURPOSE: The gastrointestinal tract is the most common site of primary extranodal non-Hodgkin lymphoma, and the prognostic factors of primary gastric diffuse large B-cell lymphoma (PG-DLBCL) differ in various studies. METHODS: We retrospectively searched for PG-DLBCL in a single institution, performed immunohistochemical analysis, classified tumor phenotype (Hans and Muris algorithms), reviewed medical records, and analyzed the clinical and immunophenotypic variables using Cox proportional hazard regression model. RESULTS: A total of 46 cases were identified including 25 males and 21 females with a median age of 63.5; 18 (39%) were at stage I and 28 (61%) at stage II. Seven (15%) patients underwent surgery as initial treatment including total (n = 3, 7%) and subtotal (n = 4, 9%) gastrectomy. Thirty-three patients (72%) received frontline chemotherapy treatment including ten with additional rituximab (MabThera) injection, and two (6%) of these patients developed perforation after chemotherapy. Four patients passed away shortly after diagnosis and the remaining three were lost to follow-up. The overall 2- and 5- year survival rates were 55% and 50%, respectively. The expression of various differentiation markers was CD10 (25%), bcl-2 (50%), bcl-6 (84%), and MUM1 (64%). Half of the cases studied (22/44) were classified as germinal center B-cell (GCB) phenotype and the remaining half as non-GCB according to Hans algorithm; 66% and 34% cases belonged to groups 1 and 2, respectively, according to Muris algorithm. Univariate analysis showed the expression of bcl-6 by the tumor cells as a favorable factor, while elevated serum lactate dehydrogenase (LDH) level, bcl-2 expression, and Muris group 2 were associated with poorer outcome. Multivariate analysis revealed that the two prognostic factors were bcl-6 expression and elevated LDH level, with hazard ratios of 0.09 (p = 0.002) and 3.72 (p = 0.024), respectively. CONCLUSION: In this retrospective study with heterogeneous treatment modality, we identified bcl-6 expression and elevated LDH level as two prognostic factors for PG-DLBCL.

[899]

TÍTULO / TITLE: - Four-arm PEG cross-linked hyaluronic acid hydrogels containing PEGylated apoptotic TRAIL protein for treating pancreatic cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Biomater. 2013 Sep 8. pii: S1742-7061(13)00438-8. doi: 10.1016/j.actbio.2013.08.046.

●● Enlace al texto completo (gratis o de pago) [1016/j.actbio.2013.08.046](#)

AUTORES / AUTHORS: - Byeon HJ; Choi SH; Choi JS; Kim I; Shin BS; Lee ES; Park ES; Lee KC; Youn YS

INSTITUCIÓN / INSTITUTION: - School of Pharmacy, Sungkyunkwan University, 300 Cheoncheon-dong, Jangan-gu, Suwon 440-746, Republic of Korea.

RESUMEN / SUMMARY: - Four-arm polyethylene glycol (PEG) cross-linked hyaluronic acid (HA) hydrogels containing PEGylated tumor necrosis factor-related apoptosis-inducing ligand (PEG-TRAIL) were fabricated, and their antitumor effects were evaluated in pancreatic cell (Mia Paca-2)-xenografted mice. HA was conjugated with 4-arm PEG10k-amine (a cross-linker) at ratios of 100:1 and 100:2 using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride as a cross-linker, and TRAIL or PEG-TRAIL was incorporated into these HA hydrogels. HA hydrogels at a 100:1 ratio were prepared in good yields (>88%), were moderately stiff, and gradually released PEG-TRAIL over approximately 14 days in vitro and over approximately 7 days in vivo (as determined by high-pressure liquid chromatography and infrared imaging). The released PEG-TRAIL was found to have obvious apoptotic activity in Mia Paca-2 cells. PEG-TRAIL HA hydrogels displayed remarkably more antitumor efficacy than TRAIL HA hydrogels in Mia Paca-2 cell-xenografted mice in terms of tumor volumes (size) and weights (453.2mm³ and 1.03g vs. 867.5mm³ and 1.86g). Furthermore, this improved antitumor efficacy was found to be due to the apoptotic activity of PEG-TRAIL in vivo (determined by a TUNEL assay) despite its substantially lower cytotoxicity than native TRAIL (IC₅₀ values: 71.8 and 202.5ngml⁻¹, respectively). This overall enhanced antitumor effect of PEG-TRAIL HA hydrogels appeared to be due to the increased stability of PEGylated TRAIL in HA hydrogels. These findings indicate that this HA hydrogel system combined with PEG-TRAIL should be considered a potential candidate for the treatment of pancreatic cancer.

[900]

TÍTULO / TITLE: - Apoptosis and necrosis of human breast cancer cells by an aqueous extract of garden cress (*Lepidium sativum*) seeds.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Saudi J Biol Sci. 2013 Apr;20(2):131-9. doi: 10.1016/j.sjbs.2012.12.002. Epub 2013 Jan 4.

●● Enlace al texto completo (gratis o de pago) [1016/j.sjbs.2012.12.002](#)

AUTORES / AUTHORS: - Mahassni SH; Al-Reemi RM

INSTITUCIÓN / INSTITUTION: - Biochemistry Department, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.

RESUMEN / SUMMARY: - Conventional treatments for breast cancer are costly and have serious side effects. Non-conventional natural treatments have gained wide acceptance due to their promise of a cure with minimal or no side effects, but little scientific evidence exists. One such common remedy is the seed of the *Lepidium sativum* plant. Presented here is the first reported use of the aqueous extract of *Lepidium sativum* seeds on breast cancer cells. The ability of the extract to induce apoptosis and necrosis in the human breast cancer cell line MCF-7, compared to normal human skin fibroblasts (HFS), was determined by morphological changes in the cells using light microscopy, DNA fragmentation assay, and fluorescent stains (Annexin V and propidium iodide) using flow cytometry and fluorescent microscopy. Apoptosis was induced in both cells, and more in MCF-7, when they were treated with 25% and 50% extract, while necrosis was observed mainly after exposure to elevated extract concentrations (75%). DNA fragmentation resulted for both cells, in a time and dose-dependent manner. Both cells, at all extract concentrations, showed no significant differences in the number of living, dead, apoptotic, and necrotic cells. Finally, the results may indicate that apoptotic changes in MCF-7 may be independent of caspase-3, which is involved in apoptosis and is lacking in MCF-7 cells.

[901]

TÍTULO / TITLE: - Involvement of post-transcriptional regulation of FOXO1 by HuR in 5-FU-induced apoptosis in breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Oncol Lett.* 2013 Jul;6(1):156-160. Epub 2013 May 17.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1352](#)

AUTORES / AUTHORS: - Li Y; Yu J; DU D; Fu S; Chen Y; Yu F; Gao P

INSTITUCIÓN / INSTITUTION: - Norman Bethune College of Medicine, Jilin University, Changchun, Jilin 130041;

RESUMEN / SUMMARY: - The post-transcriptional control of specific mRNAs is a widespread mechanism of gene regulation, which contributes to numerous biological processes in a number of cell types. The Forkhead box O (FoxO) transcription factor FOXO1 is an important tumor suppressor involved in apoptosis, the cell cycle, DNA damage repair and oxidative stress. Bioinformatic prediction identified that the 3' untranslated region (UTR) of FOXO1 is enriched with binding motifs for the human ELAV/Hu protein (HuR), indicating that FOXO1 is a potential target of HuR. Luciferase reporter assays demonstrate that HuR specifically regulates FOXO1 expression through AU-rich elements (AREs) within the FOXO1 3' UTR. Immunoprecipitation studies confirmed that HuR associates with FOXO1 mRNA in MDA-MB-231 breast cancer cells and that HuR upregulates FOXO1 mRNA levels through increased mRNA stability. Using a HuR loss- and gain-of-function approach, we revealed that FOXO1 expression was correspondingly decreased or increased in MDA-MB-231 cells. Functional assays demonstrated that HuR and FOXO1 expression levels were markedly enhanced upon 5-

fluorouracil (5-FU) stimulation in MDA-MB-231 cells. Knockdown of HuR apparently abrogated 5-FU-induced apoptosis detected by caspase-3 activities. Furthermore, in HuR knockdown cells, additional overexpression of FOXO1 moderately recovered 5-FU-induced apoptosis, which verified that HuR-modulated apoptosis upon 5-FU treatment was partially mediated by its post-transcriptional regulation of FOXO1. Therefore, modulating FOXO1 expression has been suggested to lead to the development of new therapeutic treatments for certain types of cancer.

[902]

TÍTULO / TITLE: - Oleuropein and hydroxytyrosol activate GPER/ GPR30-dependent pathways leading to apoptosis of ER-negative SKBR3 breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Nutr Food Res. 2013 Sep 9. doi: 10.1002/mnfr.201300323.

●● Enlace al texto completo (gratis o de pago) [1002/mnfr.201300323](#)

AUTORES / AUTHORS: - Chimento A; Casaburi I; Rosano C; Avena P; De Luca A; Campana C; Martire E; Santolla MF; Maggiolini M; Pezzi V; Sirianni R

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Health and Nutrition Sciences, University of Calabria, Cosenza, Italy.

RESUMEN / SUMMARY: - SCOPE: We have previously demonstrated that oleuropein (OL) and hydroxytyrosol (HT) reduce 17beta-estradiol-mediated proliferation in MCF-7 breast cancer (BC) cells without affecting the classical genomic action of estrogen receptor (ER), but activating instead the ERK1/2 pathway. Here, we hypothesized that this inhibition could be mediated by a G-protein-coupled receptor named GPER/GPR30. Using the ER-negative and GPER-positive SKBR3 BC cells as experimental model, we investigated the effects of OL and HT on GPER-mediated activation of downstream pathways. METHODS AND RESULTS: Docking simulations and ligand-binding studies evidenced that OL and HT are able to bind GPER. MTT cell proliferation assays revealed that both phenols reduced SKBR3 cell growth; this effect was abolished silencing GPER. Focusing on OL and HT GPER-mediated pathways, using Western blot analysis we showed a sustained ERK1/2 activation triggering an intrinsic apoptotic pathway. CONCLUSION: Showing that OL and HT work as GPER inverse agonists in ER-negative and GPER-positive SKBR3 BC cells, we provide novel insights into the potential of these two molecules as tools in the therapy of this subtype of BC.

[903]

TÍTULO / TITLE: - Down-Regulation of Survivin by Nemadipine-A Sensitizes Cancer Cells to TRAIL-Induced Apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomol Ther (Seoul). 2013 Jan;21(1):29-34. doi: 10.4062/biomolther.2012.088.

●● Enlace al texto completo (gratis o de pago) [4062/biomolther.2012.088](#)

AUTORES / AUTHORS: - Park SH; Park SJ; Kim JO; Shin JH; Kim ES; Jo YK; Kim JS; Park SJ; Jin DH; Hwang JJ; Lee SJ; Jeong SY; Lee C; Kim I; Cho DH

INSTITUCIÓN / INSTITUTION: - Ilsong Institute for Life Science, Hallym University, Anyang 431-060, Republic of Korea.

RESUMEN / SUMMARY: - The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the tumor necrosis factor family of cytokines. TRAIL selectively induces apoptotic cell death in various tumors and cancer cells, but it has little or no toxicity in normal cells. Agonism of TRAIL receptors has been considered to be a valuable cancer-therapeutic strategy. However, more than 85% of primary tumors are resistant to TRAIL, emphasizing the importance of investigating how to overcome TRAIL resistance. In this report, we have found that nemadipine-A, a cell-permeable L-type calcium channel inhibitor, sensitizes TRAIL-resistant cancer cells to this ligand. Combination treatments using TRAIL with nemadipine-A synergistically induced both the caspase cascade and apoptotic cell death, which were blocked by a pan caspase inhibitor (zVAD) but not by autophagy or a necrosis inhibitor. We further found that nemadipine-A, either alone or in combination with TRAIL, notably reduced the expression of survivin, an inhibitor of the apoptosis protein (IAP) family of proteins. Depletion of survivin by small RNA interference (siRNA) resulted in increased cell death and caspase activation by TRAIL treatment. These results suggest that nemadipine-A potentiates TRAIL-induced apoptosis by down-regulation of survivin expression in TRAIL resistant cells. Thus, combination of TRAIL with nemadipine-A may serve a new therapeutic scheme for the treatment of TRAIL resistant cancer cells, suggesting that a detailed study of this combination would be useful.

[904]

TÍTULO / TITLE: - Polyisoprenylated methylated protein methyl esterase is both sensitive to curcumin and overexpressed in colorectal cancer: implications for chemoprevention and treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:416534. doi: 10.1155/2013/416534. Epub 2013 Jul 1.

- [Enlace al texto completo \(gratis o de pago\) 1155/2013/416534](#)

AUTORES / AUTHORS: - Amissah F; Duverna R; Aguilar BJ; Poku RA; Lamango NS

INSTITUCIÓN / INSTITUTION: - College of Pharmacy and Pharmaceutical Sciences, Florida A&M University, Tallahassee, FL 32307, USA.

RESUMEN / SUMMARY: - Inhibition of PMPMEase, a key enzyme in the polyisoprenylation pathway, induces cancer cell death. In this study, purified PMPMEase was inhibited by the chemopreventive agent, curcumin, with a K_i of 0.3 μ M ($IC_{50} = 12.4 \mu$ M). Preincubation of PMPMEase with 1 mM curcumin followed by gel-filtration chromatography resulted in recovery of the enzyme activity, indicative of reversible inhibition. Kinetics analysis with N-para-nitrobenzoyl-S-trans,trans-farnesylcysteine

methyl ester substrate yielded K M values of 23.6 +/- 2.7 and 85.3 +/- 15.3 mu M in the absence or presence of 20 mu M curcumin, respectively. Treatment of colorectal cancer (Caco2) cells with curcumin resulted in concentration-dependent cell death with an EC50 of 22.0 mu g/mL. PMPMEase activity in the curcumin-treated cell lysate followed a similar concentration-dependent profile with IC50 of 22.6 mu g/mL. In colorectal cancer tissue microarray studies, PMPMEase immunoreactivity was significantly higher in 88.6% of cases compared to normal colon tissues (P < 0.0001). The mean scores +/- SEM were 91.7 +/- 11.4 (normal), 75.0 +/- 14.4 (normal adjacent), 294.8 +/- 7.8 (adenocarcinoma), and 310.0 +/- 22.6 (mucinous adenocarcinoma), respectively. PMPMEase overexpression in colorectal cancer and cancer cell death stemming from its inhibition is an indication of its possible role in cancer progression and a target for chemopreventive agents.

[905]

TÍTULO / TITLE: - Enhanced tumor delivery and antitumor activity in vivo of liposomal doxorubicin modified with MCF-7-specific phage fusion protein.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nanomedicine. 2013 Sep 9. pii: S1549-9634(13)00471-1. doi: 10.1016/j.nano.2013.08.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.nano.2013.08.009](#)

AUTORES / AUTHORS: - Wang T; Hartner WC; Gillespie JW; Praveen KP; Yang S; Mei LA; Petrenko VA; Torchilin VP

INSTITUCIÓN / INSTITUTION: - Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, USA.

RESUMEN / SUMMARY: - A novel strategy to improve the therapeutic index of chemotherapy has been developed by the integration of nanotechnology with phage technique. The objective of this study was to combine phage display, identifying tumor-targeting ligands, with a liposomal nanocarrier for targeted delivery of doxorubicin. Following the proof of concept in cell-based experiments, this study focused on in vivo assessment of antitumor activity and potential side-effects of phage fusion protein-modified liposomal doxorubicin. MCF-7-targeted phage-Doxil treatments led to greater tumor remission and faster onset of antitumor activity than the treatments with non-targeted formulations. The enhanced anticancer effect induced by the targeted phage-Doxil correlated with an improved tumor accumulation of doxorubicin. Tumor sections consistently revealed enhanced apoptosis, reduced proliferation activity and extensive necrosis. Phage-Doxil-treated mice did not show any sign of hepatotoxicity and maintained overall health. Therefore, MCF-7-targeted phage-Doxil seems to be an active and tolerable chemotherapy for breast cancer treatment.

[906]

TÍTULO / TITLE: - Searching in mother nature for anti-cancer activity: anti-proliferative and pro-apoptotic effect elicited by green barley on leukemia/lymphoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 9;8(9):e73508. doi: 10.1371/journal.pone.0073508.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073508](https://doi.org/10.1371/journal.pone.0073508)

AUTORES / AUTHORS: - Robles-Escajeda E; Lerma D; Nyakeriga AM; Ross JA; Kirken RA; Aguilera RJ; Varela-Ramirez A

INSTITUCIÓN / INSTITUTION: - Department of Biological Sciences and Border Biomedical Research Center, the University of Texas at El Paso, El Paso, Texas, United States of America.

RESUMEN / SUMMARY: - Green barley extract (GB) was investigated for possible anti-cancer activity by examining its anti-proliferative and pro-apoptotic properties on human leukemia/lymphoma cell lines. Our results indicate that GB exhibits selective anti-proliferative activity on a panel of leukemia/lymphoma cells in comparison to non-cancerous cells. Specifically, GB disrupted the cell-cycle progression within BJAB cells, as manifested by G2/M phase arrest and DNA fragmentation, and induced apoptosis, as evidenced by phosphatidylserine (PS) translocation to the outer cytoplasmic membrane in two B-lineage leukemia/lymphoma cell lines. The pro-apoptotic effect of GB was found to be independent of mitochondrial depolarization, thus implicating extrinsic cell death pathways to exert its cytotoxicity. Indeed, GB elicited an increase of TNF-alpha production, caspase-8 and caspase-3 activation, and PARP-1 cleavage within pre-B acute lymphoblastic leukemia Nalm-6 cells. Moreover, caspase-8 and caspase-3 activation and PARP-1 cleavage were strongly inhibited/blocked by the addition of the specific caspase inhibitors Z-VAD-FMK and Ac-DEVD-CHO. Furthermore, intracellular signaling analyses determined that GB treatment enhanced constitutive activation of Lck and Src tyrosine kinases in Nalm-6 cells. Taken together, these findings indicate that GB induced preferential anti-proliferative and pro-apoptotic signals within B-lineage leukemia/lymphoma cells, as determined by the following biochemical hallmarks of apoptosis: PS externalization, enhanced release of TNF-alpha, caspase-8 and caspase-3 activation, PARP-1 cleavage and DNA fragmentation. Our observations reveal that GB has potential as an anti-leukemia/lymphoma agent alone or in combination with standard cancer therapies and thus warrants further evaluation in vivo to support these findings.

[907]

TÍTULO / TITLE: - Expression of procaspase 3 and activated caspase 3 and its relevance in hormone-responsive gallbladder carcinoma chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Korean J Intern Med. 2013 Sep;28(5):573-8. doi: 10.3904/kjim.2013.28.5.573. Epub 2013 Aug 14.

●● Enlace al texto completo (gratis o de pago) [3904/kjim.2013.28.5.573](https://doi.org/10.1002/kjim.2013.28.5.573)

AUTORES / AUTHORS: - Maurya SK; Tewari M; Sharma B; Shukla HS

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Invertis University, Bareilly, India.

RESUMEN / SUMMARY: - BACKGROUND/AIMS: The higher incidence of gallbladder cancer (GBC) in females has been accredited to the involvement of hormones. The clinical implications of sex hormone receptors in GBC are well established. Cysteine proteases (such as caspase-3-9, etc.) are known to play a central role in the apoptotic pathway. Of these, the downstream enzyme caspase-3 is often activated in the apoptotic pathway. The aim of this work was to examine the status of apoptosis (which directly correlated with the level of active caspase-3) in hormone-responsive GBC. METHODS: We used 10 androgen receptor (AR)-positive, 14 estrogen receptor (ER)-positive, 12 HER/neu-positive, eight triple positive, and 10 triple negative malignant GBC human tissue samples. We isolated the total cellular protein from tumor tissues and carried out Western blotting using anti-pro-caspase-3 and anti-activated caspase-3 antibodies. RESULTS: ER and HER/neu-positive GBC exhibited high caspase-3 activity and low procaspase-3 activity, whereas AR-positive GBC showed no significant level of apoptosis. We also evaluated the apoptosis status of triple positive GBC and triple negative GBC, and found significant apoptosis in triple positive GBC. CONCLUSIONS: The results indicate that ER and HER/neu-positive GBCs had active apoptosis, whereas AR-positive GBC was highly resistant to apoptosis.

[908]

TÍTULO / TITLE: - Resveratrol as a Pan-HDAC Inhibitor Alters the Acetylation Status of Histone Proteins in Human-Derived Hepatoblastoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 30;8(8):e73097. doi: 10.1371/journal.pone.0073097.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073097](https://doi.org/10.1371/journal.pone.0073097)

AUTORES / AUTHORS: - Venturelli S; Berger A; Bocker A; Busch C; Weiland T; Noor S; Leischner C; Schleicher S; Mayer M; Weiss TS; Bischoff SC; Lauer UM; Bitzer M

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine I, Medical University Hospital, Tuebingen, Germany.

RESUMEN / SUMMARY: - The polyphenolic alcohol resveratrol has demonstrated promising activities for the prevention and treatment of cancer. Different modes of action have been described for resveratrol including the activation of sirtuins, which represent the class III histone deacetylases (HDACs). However, little is known about the activity of resveratrol on the classical HDACs of class I, II and IV, although these classes are involved in cancer development or progression and inhibitors of HDACs (HDACi) are currently under investigation as promising novel anticancer drugs. We could show

by in silico docking studies that resveratrol has the chemical structure to inhibit the activity of different human HDAC enzymes. In vitro analyses of overall HDAC inhibition and a detailed HDAC profiling showed that resveratrol inhibited all eleven human HDACs of class I, II and IV in a dose-dependent manner. Transferring this molecular mechanism into cancer therapy strategies, resveratrol treatment was analyzed on solid tumor cell lines. Despite the fact that hepatocellular carcinoma (HCC) is known to be particularly resistant against conventional chemotherapeutics, treatment of HCC with established HDACi already has shown promising results. Testing of resveratrol on hepatoma cell lines HepG2, Hep3B and HuH7 revealed a dose-dependent antiproliferative effect on all cell lines. Interestingly, only for HepG2 cells a specific inhibition of HDACs and in turn a histone hyperacetylation caused by resveratrol was detected. Additional testing of human blood samples demonstrated a HDACi activity by resveratrol ex vivo. Concluding toxicity studies showed that primary human hepatocytes tolerated resveratrol, whereas in vivo chicken embryotoxicity assays demonstrated severe toxicity at high concentrations. Taken together, this novel pan-HDACi activity opens up a new perspective of resveratrol for cancer therapy alone or in combination with other chemotherapeutics. Moreover, resveratrol may serve as a lead structure for chemical optimization of bioavailability, pharmacology or HDAC inhibition.

[909]

TÍTULO / TITLE: - Induction of apoptosis and cell cycle arrest in A549 human lung adenocarcinoma cells by surface encapping selenium nanoparticles: an effect enhanced by polysaccharides-protein complexes from Polyporus rhinocerus.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Agric Food Chem. 2013 Sep 20.

●● [Enlace al texto completo \(gratis o de pago\) 1021/jf403564s](#)

AUTORES / AUTHORS: - Wu H; Zhuzhu H; Li X; Li Z; Zheng W; Chen T; Yu B; Wong KH

RESUMEN / SUMMARY: - Surface-capping agents play key roles in cellular uptake and biological activity of functional nanomaterials. In the present study, functionalized selenium nanoparticles (SeNPs) have been successfully synthesized using Polyporus rhinocerus water-soluble polysaccharides-protein complexes (PRW) as the capping agent during the reduction of selenium salts. The acquired monodisperse, spherical PRW-SeNPs particles presented desirable size distribution and stability in the solution. Moreover, PRW surface decoration significantly enhanced the cellular uptake of SeNPs via endocytosis. Exposure to PRW-SeNPs significantly inhibited the growth of A549 cells through induction of apoptosis and G2/M phase arrest (IC₅₀ = 4.06 +/- 0.25 microM) supported by an increase of sub-G1 and G2/M phase cell populations, DNA fragmentation and chromatin condensation. Caspase-3/8 activation induced by PRW-SeNPs indicated that the activation of death receptors was the main cause of PRW-SeNPs-induced apoptosis. Collectively, our results suggest that it is highly efficient to

use PRW as a surface decorator of SeNPs to enhance its cellular uptake and anticancer efficacy, and the PRW-SeNPs is a potential chemopreventive agent for lung cancer therapy.

[910]

TÍTULO / TITLE: - Regulation of MLH1 mRNA and protein expression by promoter methylation in primary colorectal cancer: a descriptive and prognostic cancer marker study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Oncol (Dordr). 2013 Oct;36(5):411-9. doi: 10.1007/s13402-013-0148-2. Epub 2013 Sep 12.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13402-013-0148-2](#)

AUTORES / AUTHORS: - Jensen LH; Rasmussen AA; Byriel L; Kuramochi H; Cruger DG; Lindebjerg J; Danenberg PV; Jakobsen A; Danenberg K

INSTITUCIÓN / INSTITUTION: - Danish Colorectal Cancer Group South, University of Southern Denmark and Vejle Hospital, Vejle, Denmark, lars.henrik.jensen@rsyd.dk.

RESUMEN / SUMMARY: - **BACKGROUND:** In colorectal cancer MLH1 deficiency causes microsatellite instability, which is relevant for the patient's prognosis and treatment, and its putative heredity. Dysfunction of MLH1 is caused by sporadic gene promoter hypermethylation or by hereditary mutations as seen in Lynch Syndrome. The aim of this study was to determine in detail how DNA methylation regulates MLH1 expression and impacts clinical management. **METHODS:** Colorectal cancer samples were collected from 210 patients. The laboratory methods used to study these samples included methylation specific multiplex ligation-dependent probe amplification (MS-MLPA), real-time quantitative PCR (qPCR), and immunohistochemistry (IHC). **RESULTS:** We found that the MLH1 mRNA and protein expression levels were highly related. MS-MLPA was successful in tumors from 195 patients. In these tumors, hypermethylation was observed in promoter regions A (n = 57), B (n = 30), C (n = 28), and D (n = 47), and in intron 1 (n = 25). The promoter region C and intron 1 methylation levels were found to be excellently suited for discriminating between low and high gene expression levels, whereas those of promoter regions A, B and D were less specific. Hypermethylation in any region (n = 77) served as an independent prognostic factor (hazard ratio 0.56, 95 % confidence interval 0.36-0.89, p = 0.01). **CONCLUSIONS:** MLH1 inactivation through hypermethylation was found to be related to improved survival. Hypermethylation in promoter region C and intron 1 served as the most specific markers for this inactivation.

[911]

TÍTULO / TITLE: - Targeting colorectal cancer cells with single-walled carbon nanotubes conjugated to anticancer agent SN-38 and EGFR antibody.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomaterials. 2013 Nov;34(34):8756-65. doi: 10.1016/j.biomaterials.2013.07.067. Epub 2013 Aug 12.

●● Enlace al texto completo (gratis o de pago)

[1016/j.biomaterials.2013.07.067](#)

AUTORES / AUTHORS: - Lee PC; Chiou YC; Wong JM; Peng CL; Shieh MJ

INSTITUCIÓN / INSTITUTION: - Institute of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei 100, Taiwan.

RESUMEN / SUMMARY: - In this study, single-walled carbon nanotubes (SWNTs) conjugated with antibody C225 were used to achieve targeted therapy against EGFR over-expressed colorectal cancer cells. In addition, the control release of the chemotherapeutic drug, 7-Ethyl-10-hydroxy-camptothecin (SN38), was studied. We used three different colorectal cancer cell lines, HCT116, HT29, and SW620, listed in the order of decreasing expression levels of EGFR. Our results showed that SWNT could use C225 to specifically bind to EGFR-expressed cells. The cellular uptakes of SWNT of EGFR over-expressed cells (HCT116 and HT29) were much higher than that of the negative control (SW620). We, next, demonstrated that receptor-mediated endocytosis was the primary cell entry route for SWNT. As a consequence, abundant amount of SN38 was released and EGFR over-expressed cells were killed. The drug control release process was studied by utilizing human carboxylesterase enzyme (hCE) that would break the bond linking SN38 and SWNT-carrier in cytoplasm. The intracellular SN38 release observed by confocal microscopy showed that SN38 actually dissociated from the SWNT-carrier first. SN38's entry to nucleus was then followed while the SWNT-carrier still remained in the cytoplasm. Overall, all these data suggested that SWNT could be a good carrier for targeting controlled release therapy.

[912]

TÍTULO / TITLE: - MicroRNA-650 Was a Prognostic Factor in Human Lung Adenocarcinoma and Confers the Docetaxel Chemoresistance of Lung Adenocarcinoma Cells via Regulating Bcl-2/Bax Expression.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 21;8(8):e72615. doi: 10.1371/journal.pone.0072615.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072615](#)

AUTORES / AUTHORS: - Huang JY; Cui SY; Chen YT; Song HZ; Huang GC; Feng B; Sun M; De W; Wang R; Chen LB

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, P. R. China.

RESUMEN / SUMMARY: - Increasing evidence shows that dysregulation of microRNAs (miRNAs) is involved in malignant transformation. We investigated the clinical

significance of miR-650 and its involvement in chemoresistance to docetaxel. Our results showed that the relative expression level of miR-650 was significantly higher in LAD tissues than in corresponding nontumor tissues and high level of miR-650 expression was found to be significantly associated with high incidence of lymph node metastasis, advanced clinical stage and poor prognosis of LAD patients. Univariate and multivariate analyses indicated that high miR-650 expression was an independent prognostic factor for survival. Also, we found that the level of miR-650 in LAD tissues was correlated with the response of patients to docetaxel-based chemotherapy. Silencing of miR-650 could increase the in vitro sensitivity of docetaxel-resistant LAD cells to docetaxel, while upregulation of miR-650 decreased the sensitivity of parental LAD cells to docetaxel both in vitro and in vivo. Additionally, silencing of miR-650 could enhance the caspase-3-dependent apoptosis, which might be correlated with the decreased ratio of Bcl-2/Bax. Further researches suggested that inhibitor of growth 4 (ING4) was a direct target of miR-650. Downregulated or upregulated ING4 expression could partially rescue the effects of miR-650 inhibitor or mimics in docetaxel-resistant or parental LAD cells. Furthermore, we found that ING4 was upregulated in docetaxel-responding LAD tissues, and its expression was inversely correlated with miR-650. Thus, miR-650 is a novel prognostic marker in LAD and its expression is a potential indicator of chemosensitivity to docetaxel-based chemotherapy regimen.

[913]

TÍTULO / TITLE: - Autophagy Inhibition with Monensin Enhances Cell Cycle Arrest and Apoptosis Induced by mTOR or Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Tuberc Respir Dis (Seoul). 2013 Jul;75(1):9-17. doi: 10.4046/trd.2013.75.1.9. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [4046/trd.2013.75.1.9](#)

AUTORES / AUTHORS: - Choi HS; Jeong EH; Lee TG; Kim SY; Kim HR; Kim CH

INSTITUCIÓN / INSTITUTION: - Division of Pulmonology, Department of Internal Medicine, Korea Cancer Center Hospital, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND: In cancer cells, autophagy is generally induced as a pro-survival mechanism in response to treatment-associated genotoxic and metabolic stress. Thus, concurrent autophagy inhibition can be expected to have a synergistic effect with chemotherapy on cancer cell death. Monensin, a polyether antibiotic, is known as an autophagy inhibitor, which interferes with the fusion of autophagosome and lysosome. There have been a few reports of its effect in combination with anticancer drugs. We performed this study to investigate whether erlotinib, an epidermal growth factor receptor inhibitor, or rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, is effective in combination therapy with monensin in non-small cell lung cancer cells. METHODS: NCI-H1299 cells were treated

with rapamycin or erlotinib, with or without monensin pretreatment, and then subjected to growth inhibition assay, apoptosis analysis by flow cytometry, and cell cycle analysis on the basis of the DNA contents histogram. Finally, a Western blot analysis was done to examine the changes of proteins related to apoptosis and cell cycle control. RESULTS: Monensin synergistically increases growth inhibition and apoptosis induced by rapamycin or erlotinib. The number of cells in the sub-G1 phase increases noticeably after the combination treatment. Increase of proapoptotic proteins, including bax, cleaved caspase 3, and cleaved poly(ADP-ribose) polymerase, and decrease of anti-apoptotic proteins, bcl-2 and bcl-xL, are augmented by the combination treatment with monensin. The promoters of cell cycle progression, notch3 and skp2, decrease and p21, a cyclin-dependent kinase inhibitor, accumulates within the cell during this process. CONCLUSION: Our findings suggest that concurrent autophagy inhibition could have a role in lung cancer treatment.

[914]

TÍTULO / TITLE: - Human pancreatic cancer contains a side population expressing cancer stem cell-associated and prognostic genes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 17;8(9):e73968. doi: 10.1371/journal.pone.0073968.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073968](https://doi.org/10.1371/journal.pone.0073968)

AUTORES / AUTHORS: - Van den Broeck A; Vankelecom H; Van Delm W; Gremeaux L; Wouters J; Allemeersch J; Govaere O; Roskams T; Topal B

INSTITUCIÓN / INSTITUTION: - Department of Abdominal Surgery, University Hospitals Leuven, Leuven, Belgium ; Laboratory of Tissue Plasticity, Research Unit of Embryo and Stem Cells, Department of Development & Regeneration, University of Leuven (KU Leuven), Leuven, Belgium.

RESUMEN / SUMMARY: - In many types of cancers, a side population (SP) has been identified based on high efflux capacity, thereby enriching for chemoresistant cells as well as for candidate cancer stem cells (CSC). Here, we explored whether human pancreatic ductal adenocarcinoma (PDAC) contains a SP, and whether its gene expression profile is associated with chemoresistance, CSC and prognosis. After dispersion into single cells and incubation with Hoechst dye, we analyzed human PDAC resections specimens using flow cytometry (FACS). We identified a SP and main population (MP) in all human PDAC resection specimens (n = 52) analyzed, but detected immune (CD45(+)) and endothelial (CD31(+)) cells in this fraction together with tumor cells. The SP and MP cells, or more purified fractions depleted from CD31(+)/CD45(+) cells (pSP and pMP), were sorted by FACS and subjected to whole-genome expression analysis. This revealed upregulation of genes associated with therapy resistance and of markers identified before in putative pancreatic CSC. pSP gene signatures of 32 or 10 up- or downregulated genes were developed and tested

for discriminatory competence between pSP and pMP in different sets of PDAC samples. The prognostic value of the pSP genes was validated in a large independent series of PDAC patients (n = 78) using nCounter analysis of expression (in tumor versus surrounding pancreatic tissue) and Cox regression for disease-free and overall survival. Of these genes, expression levels of ABCB1 and CXCR4 were correlated with worse patient survival. Thus, our study for the first time demonstrates that human PDAC contains a SP. This tumor subpopulation may represent a valuable therapeutic target given its chemoresistance- and CSC-associated gene expression characteristics with potential prognostic value.

[915]

TÍTULO / TITLE: - Modeling and prediction of cytotoxicity of artemisinin for treatment of the breast cancer by using artificial neural networks.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Springerplus. 2013;2:340. doi: 10.1186/2193-1801-2-340.

●● Enlace al texto completo (gratis o de pago) [1186/2193-1801-2-340](#)

AUTORES / AUTHORS: - Qaderi A; Dadgar N; Mansouri H; Alavi SE; Esfahani MK; Akbarzadeh A

INSTITUCIÓN / INSTITUTION: - Department of Chemical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran.

RESUMEN / SUMMARY: - While artemisinin is known as anticancer medication with favorable remedial effects, its side effects must not be neglected. In order to reduce such side effects and increase artemisinin therapeutic index, nano technology has been considered as a new approach. Liposome preparation is supposed to be one of the new methods of drug delivery. To prepare the desired nanoliposome, certain proportions of phosphatidylcholine, cholesterol and artemisinin are mixed together. Besides, in order to achieve more stability, the formulation was pegylated by polyethylene glycol 2000 (PEG 2000). Mean diameter of nanoliposomes was determined by means of Zeta sizer. Encapsulation was calculated 96.02% in nanoliposomal and 91.62% in pegylated formulation. Compared to pegylated formulation, the percent of released drug in nanoliposomal formulation was more. In addition, this study reveals that cytotoxicity effect of pegylated nanoliposomal artemisinin was more than nanoliposomal artemisinin. Since artificial neural network shows high possibility of nonlinear modulation, it is used to predict cytotoxicity effect in this study, which can precisely indicate the cytotoxicity and IC50 of anticancer drugs.

[916]

TÍTULO / TITLE: - Optimization of cytarabine (ARA-C) therapy for acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Exp Hematol. %8?(3k+]3s medicinedirect.com/journal ●●

Experimental Hematology: <> Oncol. 2013 Aug 6;2(1):20.

●● Enlace al texto completo (gratis o de pago) 1186/2162-3619-2-20

AUTORES / AUTHORS: - Momparler RL

RESUMEN / SUMMARY: - Cytarabine (cytosine arabinoside) is one of the most effective drugs for the treatment of acute myeloid leukemia. The standard dose of cytarabine used to treat this leukemia is 100 mg per square meter. In an attempt to improve the effectiveness of cytarabine against acute myeloid leukemia, a high-dose treatment (3,000 mg per square meter) was introduced into therapy. The side effects of high-dose cytarabine was a major concern, especially its neurological toxicity. A review of recent clinical trials indicates that this high-dose cytarabine can be replaced by the intermediate-dose of 1,000 mg per square meter without loss of efficacy and with less toxicity. This is an important step to improve the efficacy of cytarabine for the treatment of acute myeloid leukemia. Despite the improvements in the therapy for this leukemia, the current overall survival rate for adult patients is less than 30%. To optimize the cytarabine therapy, it is important to determine how some leukemic stem cells survive treatment. Preclinical data suggest that survival of the leukemic stem cells could be due to the long 12 hour interval between infusions of cytarabine, which permits some leukemic cells to escape its S phase specific action. Among the other factors that can lead to leukemic cell survival are the high levels in the liver and spleen of cytidine deaminase, the enzyme that inactivates cytarabine and drug resistance due to deficiency in deoxycytidine kinase, the enzyme that activates the prodrug, cytarabine. Several approaches are proposed in this commentary to overcome these impediments with the goal of increasing the effectiveness of cytarabine for the treatment of acute myeloid leukemia.

[917]

TÍTULO / TITLE: - Cadmium Induced Cell Apoptosis, DNA Damage, Decreased DNA Repair Capacity, and Genomic Instability during Malignant Transformation of Human Bronchial Epithelial Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Med Sci. 2013 Aug 30;10(11):1485-96. doi: 10.7150/ijms.6308.

●● Enlace al texto completo (gratis o de pago) 7150/ijms.6308

AUTORES / AUTHORS: - Zhou Z; Wang C; Liu H; Huang Q; Wang M; Lei Y

INSTITUCIÓN / INSTITUTION: - 1. School of public health, Guangzhou Medical University, Guangzhou 510182, People's Republic of China.

RESUMEN / SUMMARY: - Cadmium and its compounds are well-known human carcinogens, but the mechanisms underlying the carcinogenesis are not entirely understood. Our study was designed to elucidate the mechanisms of DNA damage in cadmium-induced malignant transformation of human bronchial epithelial cells. We analyzed cell cycle, apoptosis, DNA damage, gene expression, genomic instability, and

the sequence of exons in DNA repair genes in several kinds of cells. These cells consisted of untreated control cells, cells in the fifth, 15th, and 35th passage of cadmium-treated cells, and tumorigenic cells from nude mice using flow cytometry, Hoechst 33258 staining, comet assay, quantitative real-time polymerase chain reaction (PCR), Western blot analysis, random amplified polymorphic DNA (RAPD)-PCR, and sequence analysis. We observed a progressive increase in cell population of the G0/G1 phase of the cell cycle and the rate of apoptosis, DNA damage, and cadmium-induced apoptotic morphological changes in cerebral cortical neurons during malignant transformation. Gene expression analysis revealed increased expression of cell proliferation (PCNA), cell cycle (CyclinD1), pro-apoptotic activity (Bax), and DNA damage of the checkpoint genes ATM, ATR, Chk1, Chk2, Cdc25A. Decreased expression of the anti-apoptotic gene Bcl-2 and the DNA repair genes hMSH2, hMLH1, ERCC1, ERCC2, and hOGG1 was observed. RAPD-PCR revealed genomic instability in cadmium-exposed cells, and sequence analysis showed mutation of exons in hMSH2, ERCC1, XRCC1, and hOGG1 in tumorigenic cells. This study suggests that Cadmium can increase cell apoptosis and DNA damage, decrease DNA repair capacity, and cause mutations, and genomic instability leading to malignant transformation. This process could be a viable mechanism for cadmium-induced cancers.

[918]

TÍTULO / TITLE: - ERG Protein Expression Is of Limited Prognostic Value in Men with Localized Prostate Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ISRN Urol. 2013 Aug 19;2013:786545. doi: 10.1155/2013/786545.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/786545](#)

AUTORES / AUTHORS: - Teng LH; Wang C; Dolph M; Donnelly B; Bismar TA

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Calgary, AB, Canada T2V 1P9.

RESUMEN / SUMMARY: - Background. The prognostic significance of ERG expression in prostate cancer (PCA) has generated mixed results. We sought to investigate the prognostic significance of ERG expression in a localized cohort of men with PCA. Material and Methods. We investigated ERG protein expression in a cohort of 198 men with localized PCA. ERG expression was correlated with patients' clinical outcome and several pathological parameters, including Gleason score (GS), pathological stage, surgical margin, and extra-capsular extension. Results. ERG expression was detected in 86/198 (43.4%) patients exclusively in neoplastic epithelium. Overall, ERG mean expression intensity was 1.01 +/- 1.27 versus 0.37 +/- 0.83 in acinar PCA compared to foamy type PCA (P < 0.001). In HGPIN, ERG intensity levels were comparable to those in foamy type PCA (0.13 +/- 0.56) but significantly lower than those in acinar PCA (P < 0.001). ERG expression was significantly associated with extra-prostatic extension and higher pathological stage and showed a trend toward seminal vesicle invasion. Herein,

ERG expression was documented in 50/131 (38.1%) patients with pT2 versus 30/55 (54.5%) patients with pT3 (P = 0.04). ERG association with higher pathological stage was more pronounced in patients with GS > 7. Grouping patients into those with GS <= 7 versus >7, there was no significant association between ERG expression and GS. Similarly, no association was present in relation to either surgical margins or postsurgical serum PSA levels. Conclusion. We report significant association between ERG protein levels and extra-prostatic extension and higher pathological stage. ERG expression is not associated with adverse clinical outcome and is of limited prognostic value in localized PCA.

[919]

TÍTULO / TITLE: - Is IL-2 still indicated for melanoma and RCC? What a question to ask!

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncology (Williston Park). 2013 Jul;27(7):695, 701.

AUTORES / AUTHORS: - Hamid O

INSTITUCIÓN / INSTITUTION: - Melanoma Clinic, The Angeles Clinic and Research Institute, Los Angeles, California, USA.

[920]

TÍTULO / TITLE: - Growth Inhibitory Effect of (E)-2,4-bis(p-hydroxyphenyl)-2-Butenal Diacetate through Induction of Apoptotic Cell Death by Increasing DR3 Expression in Human Lung Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomol Ther (Seoul). 2012 Nov;20(6):538-43. doi: 10.4062/biomolther.2012.20.6.538.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[4062/biomolther.2012.20.6.538](#)

AUTORES / AUTHORS: - Lee US; Ban JO; Yeon ET; Lee HP; Udumula V; Ham YW; Hong JT

INSTITUCIÓN / INSTITUTION: - Department of Food Science & Technology, Korea National University of Transportation, Jeungpyeong 368-701, Republic of Korea.

RESUMEN / SUMMARY: - The Maillard Reaction Products (MRPs) are chemical compounds which have been known to be effective in chemoprevention. Death receptors (DR) play a central role in directing apoptosis in several cancer cells. In our previous study, we demonstrated that (E)-2,4-bis(p-hydroxyphenyl)-2-butenal, a MRP product, inhibited human colon cancer cell growth by inducing apoptosis via nuclear factor-kappaB (NF-kappaB) inactivation and G2/M phase cell cycle arrest. In this study, (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate, a new (E)-2,4-bis(p-hydroxyphenyl)-2-butenal derivative, was synthesized to improve their solubility and stability in water and then evaluated against NCI-H460 and A549 human lung cancer cells. (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate reduced the viability in both cell lines in a time and dose-dependent manner. We also found that (E)-2,4-bis(p-hydroxyphenyl)-2-

butenal diacetate increased apoptotic cell death through the upregulation of the expression of death receptor (DR)-3 and DR6 in both lung cancer cell lines. In addition to this, the transfection of DR3 siRNA diminished the growth inhibitory and apoptosis inducing effect of (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate on lung cancer cells, however these effects of (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate was not changed by DR6 siRNA. These results indicated that (E)-2,4-bis(p-hydroxyphenyl)-2-butenal diacetate inhibits human lung cancer cell growth via increasing apoptotic cell death by upregulation of the expression of DR3.

[921]

TÍTULO / TITLE: - BAD Dephosphorylation and Decreased Expression of MCL-1 Induce Rapid Apoptosis in Prostate Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 5;8(9):e74561. doi: 10.1371/journal.pone.0074561.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0074561](https://doi.org/10.1371/journal.pone.0074561)

AUTORES / AUTHORS: - Yancey D; Nelson KC; Baiz D; Hassan S; Flores A; Pullikuth A; Karpova Y; Axanova L; Moore V; Sui G; Kulik G

INSTITUCIÓN / INSTITUTION: - Department of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, North Carolina, United States of America.

RESUMEN / SUMMARY: - PTEN loss and constitutive activation of the PI3K signaling pathway have been associated with advanced androgen-independent prostate cancer. PTEN-deficient prostate cancer C42Luc cells survive in serum-free media and show relative resistance to apoptosis even in the presence of the PI3K inhibitor ZSTK474. Yet, when ZSTK474 is combined with the translation inhibitor cycloheximide, C42Luc cells undergo apoptosis within 6 hours. We identified dephosphorylation of BAD (Bcl2-associated death promoter) as a main apoptosis-regulatory molecule downstream from PI3K, and loss of MCL-1 (Myeloid cell leukemia -1) as a major target of cycloheximide. The combination of MCL-1 knockdown and expression of phosphorylation-deficient mutant BAD2SA is sufficient to trigger rapid apoptosis in prostate cancer cells. These results establish the mechanism for the synergistic induction of apoptosis by the combination of a PI3K inhibitor and of a protein synthesis inhibitor in PTEN-deficient prostate cancer cells.

[922]

TÍTULO / TITLE: - Therapeutic Silencing of Bcl-2 by Systemically Administered siRNA Nanotherapeutics Inhibits Tumor Growth by Autophagy and Apoptosis and Enhances the Efficacy of Chemotherapy in Orthotopic Xenograft Models of ER (-) and ER (+) Breast Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Ther Nucleic Acids. 2013 Sep 10;2:e121. doi: 10.1038/mtna.2013.45.

●● Enlace al texto completo (gratis o de pago) [1038/mtna.2013.45](https://doi.org/10.1038/mtna.2013.45)

AUTORES / AUTHORS: - Tekedereli I; Alpay SN; Akar U; Yuca E; Ayugo-Rodriguez C; Han HD; Sood AK; Lopez-Berestein G; Ozpolat B

INSTITUCIÓN / INSTITUTION: - Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, USA.

RESUMEN / SUMMARY: - Bcl-2 is overexpressed in about a half of human cancers and 50-70% of breast cancer patients, thereby conferring resistance to conventional therapies and making it an excellent therapeutic target. Small interfering RNA (siRNA) offers novel and powerful tools for specific gene silencing and molecularly targeted therapy. Here, we show that therapeutic silencing of Bcl-2 by systemically administered nanoliposomal (NL)-Bcl-2 siRNA (0.15 mg siRNA/kg, intravenous) twice a week leads to significant antitumor activity and suppression of growth in both estrogen receptor-negative (ER(-)) MDA-MB-231 and ER-positive (+) MCF7 breast tumors in orthotopic xenograft models (P < 0.05). A single intravenous injection of NL-Bcl-2-siRNA provided robust and persistent silencing of the target gene expression in xenograft tumors. NL-Bcl-2-siRNA treatment significantly increased the efficacy of chemotherapy when combined with doxorubicin in both MDA-MB-231 and MCF-7 animal models (P < 0.05). NL-Bcl-2-siRNA treatment-induced apoptosis and autophagic cell death, and inhibited cyclin D1, HIF1alpha and Src/Fak signaling in tumors. In conclusion, our data provide the first evidence that in vivo therapeutic targeting Bcl-2 by systemically administered nanoliposomal-siRNA significantly inhibits growth of both ER(-) and ER(+) breast tumors and enhances the efficacy of chemotherapy, suggesting that therapeutic silencing of Bcl-2 by siRNA is a viable approach in breast cancers. Molecular Therapy- Nucleic Acids (2013) 2, e121; doi:10.1038/mtna.2013.45; published online 10 September 2013.

[923]

TÍTULO / TITLE: - Nimotuzumab enhances the radiosensitivity of cancer cells in vitro by inhibiting radiation-induced DNA damage repair.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 16;8(8):e70727. doi: 10.1371/journal.pone.0070727.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070727](https://doi.org/10.1371/journal.pone.0070727)

AUTORES / AUTHORS: - Qu YY; Hu SL; Xu XY; Wang RZ; Yu HY; Xu JY; Chen L; Dong GL

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, the Third Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China.

RESUMEN / SUMMARY: - BACKGROUND: Nimotuzumab is a humanized IgG1 monoclonal antibody specifically targeting EGFR. In this study, we aimed to investigate the

molecular mechanisms of nimotuzumab in its effects of enhancing cancer cell radiosensitivity. PRINCIPAL FINDING: Lung cancer A549 cells and breast cancer MCF-7 cells were pretreated with or without nimotuzumab for 24 h before radiation to perform the clonogenic survival assay and to analyze the cell apoptosis by flow cytometry. gamma-H2AX foci were detected by confocal microscopy to assess the effect of nimotuzumab on radiation induced DNA repair. EGFR activation was examined and the levels of DNA damage repair related proteins in A549 cells at different time point and at varying doses exposure after nimotuzumab and radiation treatment were examined by Western blot. Pretreatment with nimotuzumab reduced clonogenic survival after radiation, inhibited radiation-induced EGFR activation and increased the radiation-induced apoptosis in both A549 cells and MCF-7 cells. The foci of gamma-H2AX 24 h after radiation significantly increased in nimotuzumab pretreated cells with different doses. The phosphorylation of AKT and DNA-PKcs were remarkably inhibited in the combination group at each dose point as well as time point. CONCLUSIONS: Our results revealed that the possible mechanism of nimotuzumab enhancing the cancer radiosensitivity is that nimotuzumab inhibited the radiation-induced activation of DNA-PKcs through blocking the PI3K/AKT pathway, which ultimately affected the DNA DSBs repair.

[924]

TÍTULO / TITLE: - Candidate Markers That Associate with Chemotherapy Resistance in Breast Cancer through the Study on Taxotere-Induced Damage to Tumor Microenvironment and Gene Expression Profiling of Carcinoma-Associated Fibroblasts (CAFs).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e70960. doi: 10.1371/journal.pone.0070960.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0070960](#)

AUTORES / AUTHORS: - Rong G; Kang H; Wang Y; Hai T; Sun H

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Xuanwu Hospital, Capital Medical University, Beijing, P. R. China.

RESUMEN / SUMMARY: - Recently, emerging evidence has suggested that carcinoma-associated fibroblasts (CAFs) could contribute to chemotherapy resistances in breast cancer treatment. The aim of this study is to compare the gene expression profiling of CAFs before and after chemotherapy and pick up candidate genes that might associate with chemotherapy resistance and could be used as predictors of treatment response. CAFs were cultured from surgically resected primary breast cancers and identified with immunohistochemistry (IHC) and Flow cytometry (FCM). MDA-MB-231 cells were cultured as the breast cancer cell line. Cell adhesion assay, invasion assay, and proliferation assay (MTT) were performed to compare the function of MDA-MB-231 cells co-cultured with CAFs and MDA-MB-231 cells without co-culture, after chemotherapy. Totally 6 pairs of CAFs were prepared for microarray analysis. Each pair

of CAFs were obtained from the same patient and classified into two groups. One group was treated with Taxotere (regarded as after chemotherapy) while the other group was not processed with Taxotere (regarded as before chemotherapy). According to our study, the primary-cultured CAFs exhibited characteristic phenotype. After chemotherapy, MDA-MB-231 cells co-cultured with CAFs displayed increasing adhesion, invasiveness and proliferation abilities, compared with MDA-MB-231 cells without CAFs. Moreover, 35 differentially expressed genes (absolute fold change >2) were identified between CAFs after chemotherapy and before chemotherapy, including 17 up-regulated genes and 18 down-regulated genes. CXCL2, MMP1, IL8, RARRES1, FGF1, and CXCR7 were picked up as the candidate markers, of which the differential expression in CAFs before and after chemotherapy was confirmed. The results indicate the changes of gene expression in CAFs induced by Taxotere treatment and propose the candidate markers that possibly associate with chemotherapy resistance in breast cancer.

[925]

TÍTULO / TITLE: - Predictors of mother and child DNA yields in buccal cell samples collected in pediatric cancer epidemiologic studies: a report from the Children's Oncology group.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Genet. 2013 Aug 12;14(1):69.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1471-2156-14-69](#)

AUTORES / AUTHORS: - Poynter JN; Ross JA; Hooten AJ; Langer E; Blommer C; Spector LG

RESUMEN / SUMMARY: - BACKGROUND: Collection of high-quality DNA is essential for molecular epidemiology studies. Methods have been evaluated for optimal DNA collection in studies of adults; however, DNA collection in young children poses additional challenges. Here, we have evaluated predictors of DNA quantity in buccal cells collected for population-based studies of infant leukemia (N = 489 mothers and 392 children) and hepatoblastoma (HB; N = 446 mothers and 412 children) conducted through the Children's Oncology Group. DNA samples were collected by mail using mouthwash (for mothers and some children) and buccal brush (for children) collection kits and quantified using quantitative real-time PCR. Multivariable linear regression models were used to identify predictors of DNA yield. RESULTS: Median DNA yield was higher for mothers in both studies compared with their children (14 mug vs. <1 mug). Significant predictors of DNA yield in children included case—control status (beta = - 0.69, 50% reduction, P = 0.01 for case vs. control children), brush collection type, and season of sample collection. Demographic factors were not strong predictors of DNA yield in mothers or children in this analysis. CONCLUSIONS: The association with seasonality suggests that conditions during transport may influence DNA yield. The low yields observed in most children in these studies highlight the importance of developing alternative methods for DNA collection in younger age groups.

[926]

TÍTULO / TITLE: - Nonsmall cell lung cancer therapy: insight into multitargeted small-molecule growth factor receptor inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:964743. doi: 10.1155/2013/964743. Epub 2013 Jul 1.

●● Enlace al texto completo (gratis o de pago) [1155/2013/964743](#)

AUTORES / AUTHORS: - Roy M; Luo YH; Ye M; Liu J

INSTITUCIÓN / INSTITUTION: - Molecular Biology Research Center, School of Life Science and State Key Laboratory of Medical Genetics of China, Central South University, Changsha, Hunan 410078, China.

RESUMEN / SUMMARY: - To date, lung cancer is the leading cause of cancer-related death worldwide, among which nonsmall cell lung cancer (NSCLC) comprises about 85%. Taking into account the side effects of surgery, radiation, platinum-based doublet chemotherapy, and the growth self-sufficiency characteristic of cancer cells, drugs have been discovered toward growth factor receptor (GFR) to treat NSCLC. As expected, these drugs provide a greater benefit. To increase the efficacy of such growth factor receptor tyrosine kinase inhibitors (RTKIs), coinhibition of GFR signaling pathways and combination of inhibitors along with radiation or chemotherapy have drew intense insight. Although clinical trials about single-agent RTKIs or their combination strategies suggest their increase potency against cancer, they are not beyond adverse effects, and sometimes the effects are more deadly than chemotherapy. Nevertheless the hope for RTKIs may be proved true by further researches and digging deep into cancer therapeutics.

[927]

TÍTULO / TITLE: - A preliminary study of imaging paclitaxel-induced tumor apoptosis with (99)Tc(m)-His10-Annexin V.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin Med J (Engl). 2013;126(15):2928-33.

AUTORES / AUTHORS: - Zheng YM; Wang F; Fang W; Hua ZC; Wang ZZ; Meng QL; Yan J

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, China-Japan Friendship Hospital, Beijing 100029, China.

RESUMEN / SUMMARY: - BACKGROUND: In tumors the process of apoptosis occurs over an interval of time after chemotherapy. It is important to determine the best time for detecting apoptosis by in vivo imaging. In this study, we evaluated the dynamics and feasibility of imaging non-small cell lung cancer (NSCLC) apoptosis induced by paclitaxel treatment using a (99)Tc(m)-labeled Annexin V recombinant with ten consecutive histidines (His10-Annexin V) in a mouse model. METHODS: (99)Tc(m)-His10-Annexin V was prepared by one step direct labeling; radio-chemical purity (RCP)

and radio-stability was tested. The binding of (99)Tc(m)-His10-Annexin V to apoptotic cells was validated in vitro using camptothecin-induced Jurkat cells. In vivo bio-distribution was determined in mice by dissection. The human H460 NSCLC tumor cell line (H460) tumor-bearing mice were treated with intravenous paclitaxel 24, 48 and 72 hours later. (99)Tc(m)-His10-Annexin V was injected intravenously, and planar images were acquired at 2, 4 and 6 hours post-injection on a dual-head gamma camera fitted with a pinhole collimator. Tumor-to-normal tissue ratios (T/NT) were calculated by ROI analysis and they reflected specific binding of (99)Tc(m)-His10-Annexin V. Mice were sacrificed after imaging. Caspase-3, as the apoptosis detector, was determined by flow cytometry, and DNA fragmentation was analyzed by the terminal deoxynucleotidyltransferase mediated dUTP nick-end labeling (TUNEL) assay. Nonspecific accumulation of protein was estimated using bovine serum albumin (BSA). The imaging data were correlated with TUNEL-positive nuclei and caspase-3 activity. RESULTS: (99)Tc(m)-His10-Annexin V had a RCP > 98% and high stability 2 hours after radio-labeling, and it could bind to apoptotic cells with high affinity. Bio-distribution of (99)Tc(m)-His10-Annexin V showed predominant uptake in kidney, relatively low uptake in myocardium, liver and gastrointestinal tract, and rapid clearance from blood and kidney was observed. The T/NT was significantly increased after paclitaxel treatment, whereas it was low in untreated tumors (T/NT = 1.43 +/- 0.18). The %ID/g activity in Group 2 (24 hours), Group 3 (48 hours) and Group 4 (72 hours) after treatment was 2.55 +/- 0.73, 3.35 +/- 1.10, and 3.4 +/- 0.96, respectively. Whereas in the non-treated group, Group 1, %ID/g was 1.10 +/- 0.18. The radiotracer uptake was positively correlated to the apoptotic index ($r = 0.852$, $P < 0.01$), as well as caspase-3 activity ($r = 0.816$, $P < 0.01$). CONCLUSION: This study addresses the dynamics and feasibility of imaging non-small cell lung tumor apoptosis using (99)Tc(m)- His10-Annexin V.

[928]

TÍTULO / TITLE: - Using Evolutional Properties of Gene Networks in Understanding Survival Prognosis of Glioblastoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - IEEE J Biomed Health Inform. 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [1109/JBHI.2013.2282569](#)

AUTORES / AUTHORS: - Upton A; Arvanitis T

RESUMEN / SUMMARY: - Previously, we investigated survival prognosis of glioblastoma by applying a gene regulatory approach to a human glioblastoma dataset. Here, we further extend our understanding of survival prognosis of glioblastoma by refining the network inference technique we apply to the glioblastoma dataset with the intent of uncovering further topological properties of the networks. For this work, we modify the approach by specifically looking at both positive and negative correlations

separately, as oppose to absolute correlations. There is great interest in applying mathematical modeling approaches to cancer cell line datasets to generate network models of gene regulatory interactions. Analysis of these networks using graph theory metrics can identify genes of interest. The principal approach for modeling microarray datasets has been to group all the cell lines together into one overall network, and then analyze this network as a whole. As per the previous study, we categorize a human glioblastoma cell line data set into five categories based on survival data, and analyze each category separately using both negative and positive correlation networks constructed using a modified version of the WGCNA algorithm. Using this approach, we identified a number of genes as being important across different survival stages of the glioblastoma cell lines.

[929]

TÍTULO / TITLE: - Durable Remission of Mantle Cell Lymphoma Relapsing a Third Time After Allogeneic Hematopoietic Stem Cell Transplantation Treated With Rituximab, Bortezomib, Donor Lymphocytes, and Pegylated Interferon.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Aug 29. pii: S2152-2650(13)00223-1. doi: 10.1016/j.clml.2013.05.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.clml.2013.05.006](#)

AUTORES / AUTHORS: - Vo P; Jaffe ES; Cook L; Ramos C; Childs R

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Newark Beth Israel Medical Center, Newark, NJ. Electronic address: uyenphuong18@yahoo.com.

[930]

TÍTULO / TITLE: - A Genome-Wide Systematic Analysis Reveals Different and Predictive Proliferation Expression Signatures of Cancerous vs. Non-Cancerous Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS Genet. 2013 Sep;9(9):e1003806. doi: 10.1371/journal.pgen.1003806. Epub 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pgen.1003806](#)

AUTORES / AUTHORS: - Waldman YY; Geiger T; Ruppin E

INSTITUCIÓN / INSTITUTION: - The Blavatnik School of Computer Science, Tel Aviv University, Tel Aviv, Israel.

RESUMEN / SUMMARY: - Understanding cell proliferation mechanisms has been a long-lasting goal of the scientific community and specifically of cancer researchers. Previous genome-scale studies of cancer proliferation determinants have mainly relied on knockdown screens aimed to gauge their effects on cancer growth. This powerful approach has several limitations such as off-target effects, partial knockdown, and masking effects due to functional backups. Here we employ a complementary approach and assign each gene a cancer Proliferation Index (cPI) that quantifies the

association between its expression levels and growth rate measurements across 60 cancer cell lines. Reassuringly, genes found essential in cancer gene knockdown screens exhibit significant positive cPI values, while tumor suppressors exhibit significant negative cPI values. Cell cycle, DNA replication, splicing and protein production related processes are positively associated with cancer proliferation, while cellular migration is negatively associated with it - in accordance with the well known “go or grow” dichotomy. A parallel analysis of genes’ non-cancerous proliferation indices (nPI) across 224 lymphoblastoid cell lines reveals surprisingly marked differences between cancerous and non-cancerous proliferation. These differences highlight genes in the translation and spliceosome machineries as selective cancer proliferation-associated proteins. A cross species comparison reveals that cancer proliferation resembles that of microorganisms while non-cancerous proliferation does not. Furthermore, combining cancerous and non-cancerous proliferation signatures leads to enhanced prediction of patient outcome and gene essentiality in cancer. Overall, these results point to an inherent difference between cancerous and non-cancerous proliferation determinants, whose understanding may contribute to the future development of novel cancer-specific anti-proliferative drugs.

[931]

TÍTULO / TITLE: - Identification of upstream regulators for prognostic expression signature genes in colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Syst Biol. 2013 Sep 4;7(1):86.

●● Enlace al texto completo (gratis o de pago) [1186/1752-0509-7-86](#)

AUTORES / AUTHORS: - Bae T; Rho K; Choi JW; Horimoto K; Kim W; Kim S

RESUMEN / SUMMARY: - BACKGROUND: Gene expression signatures have been commonly used as diagnostic and prognostic markers for cancer subtyping. However, expression signatures frequently include many passengers, which are not directly related to cancer progression. Their upstream regulators such as transcription factors (TFs) may take a more critical role as drivers or master regulators to provide better clues on the underlying regulatory mechanisms and therapeutic applications. RESULTS: In order to identify prognostic master regulators, we took the known 85 prognostic signature genes for colorectal cancer and inferred their upstream TFs. To this end, a global transcriptional regulatory network was constructed with total >200,000 TF-target links using the ARACNE algorithm. We selected the top 10 TFs as candidate master regulators to show the highest coverage of the signature genes among the total 846 TF-target sub-networks or regulons. The selected TFs showed a comparable or slightly better prognostic performance than the original 85 signature genes in spite of greatly reduced number of marker genes from 85 to 10. Notably, these TFs were selected solely from inferred regulatory links using gene expression profiles and included many TFs regulating tumorigenic processes such as proliferation, metastasis,

and differentiation. CONCLUSIONS: Our network approach leads to the identification of the upstream transcription factors for prognostic signature genes to provide leads to their regulatory mechanisms. We demonstrate that our approach could identify upstream biomarkers for a given set of signature genes with markedly smaller size and comparable performances. The utility of our method may be expandable to other types of signatures such as diagnosis and drug response.

[932]

TÍTULO / TITLE: - Combined upregulation of matrix metalloproteinase-1 and proteinase-activated receptor-1 predicts unfavorable prognosis in human nasopharyngeal carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Aug 20;6:1139-46. doi: 10.2147/OTT.S50389.

●● Enlace al texto completo (gratuito o de pago) [2147/OTT.S50389](#)

AUTORES / AUTHORS: - Yang R; Xu Y; Li P; Zhang X; Wang J; Gu D; Wang Y

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Cancer Biology, Cell Engineering Research Center and Department of Cell Biology, Department of Clinical Nursing, School of Nursing, The Fourth Military Medical University, Xi'an, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: The upregulation of matrix metalloproteinase-1 (MMP-1) has been demonstrated to be correlated with lymph node metastasis of nasopharyngeal carcinoma (NPC), while the activation of protease-activated receptor-1 (PAR-1) mediates proliferation and invasion of NPC cells. The present study investigated the clinical significance of the coexpression of MMP-1 and PAR-1 in NPC patients in determining the prognosis. METHODS: Immunohistochemistry was performed to detect the expression of MMP-1 and PAR-1 in tumor tissue samples from 266 NPC patients. RESULTS: Overexpression of MMP-1 and PAR-1 proteins were, respectively, detected in 190 (71.43%) and 182 (68.42%) of the 266 NPC patients. In addition, the combined MMP-1 and PAR-1 expression was significantly associated with advanced T-stage ($P = 0.01$), advanced clinical stage ($P = 0.002$), positive recurrence ($P = 0.01$), and metastatic status ($P = 0.01$) of NPC. Moreover, the overall survival in NPC patients with MMP-1 and PAR-1 dual overexpression was significantly shorter than in those with dual low expression ($P < 0.001$). Furthermore, the multivariate analyses indicated that the combined MMP-1 and PAR-1 overexpression was an independent prognostic factor for overall survival ($P = 0.001$) in NPC patients, but the upregulation of MMP-1 and PAR-1 alone was, in each case, not an independent prognostic factor for this disease. CONCLUSION: Our data provide convincing evidence, for the first time, that the activation of the MMP-1 and PAR-1 axis may be involved in the tumorigenesis and progression of NPC. The upregulation of MMP-1 in combination with PAR-1

overexpression is an unfavorable prognostic marker for NPC and might offer the possibility of future therapeutic targets.

[933]

TÍTULO / TITLE: - Mutant p53-Notch1 Signaling Axis Is Involved in Curcumin-Induced Apoptosis of Breast Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Korean J Physiol Pharmacol. 2013 Aug;17(4):291-7. doi: 10.4196/kjpp.2013.17.4.291. Epub 2013 Jul 30.

●● [Enlace al texto completo \(gratis o de pago\) 4196/kjpp.2013.17.4.291](#)

AUTORES / AUTHORS: - Bae YH; Ryu JH; Park HJ; Kim KR; Wee HJ; Lee OH; Jang HO; Bae MK; Kim KW; Bae SK

INSTITUCIÓN / INSTITUTION: - Department of Dental Pharmacology, School of Dentistry, Yangsan Campus of Pusan National University, Yangsan 626-870, Korea.

RESUMEN / SUMMARY: - Notch1 has been reported to be highly expressed in triple-negative and other subtypes of breast cancer. Mutant p53 (R280K) is overexpressed in MDA-MB-231 triple-negative human breast cancer cells. The present study aimed to determine whether the mutant p53 can be a potent transcriptional activator of the Notch1 in MDA-MB-231 cells, and explore the role of this mutant p53-Notch1 axis in curcumin-induced apoptosis. We found that curcumin treatment resulted in an induction of apoptosis in MDA-MB-231 cells, together with downregulation of Notch1 and its downstream target, Hes1. This reduction in Notch1 expression was determined to be due to the decreased activity of endogenous mutant p53. We confirmed the suppressive effect of curcumin on Notch1 transcription by performing a Notch1 promoter-driven reporter assay and identified a putative p53-binding site in the Notch1 promoter by EMSA and chromatin immunoprecipitation analysis. Overexpression of mutant p53 increased Notch1 promoter activity, whereas knockdown of mutant p53 by small interfering RNA suppressed Notch1 expression, leading to the induction of cellular apoptosis. Moreover, curcumin-induced apoptosis was further enhanced by the knockdown of Notch1 or mutant p53, but it was decreased by the overexpression of active Notch1. Taken together, our results demonstrate, for the first time, that Notch1 is a transcriptional target of mutant p53 in breast cancer cells and suggest that the targeting of mutant p53 and/or Notch1 may be combined with a chemotherapeutic strategy to improve the response of breast cancer cells to curcumin.

[934]

TÍTULO / TITLE: - Combination of intratumoral invariant natural killer T cells and interferon-gamma is associated with prognosis of hepatocellular carcinoma after curative resection.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e70345. doi: 10.1371/journal.pone.0070345. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070345](https://doi.org/10.1371/journal.pone.0070345)

AUTORES / AUTHORS: - Xiao YS; Gao Q; Xu XN; Li YW; Ju MJ; Cai MY; Dai CX; Hu J; Qiu SJ; Zhou J; Fan J

INSTITUCIÓN / INSTITUTION: - Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, P. R. China ; Key Laboratory for Carcinogenesis and Cancer Invasion, Ministry of Education, Shanghai, P. R. China.

RESUMEN / SUMMARY: - **PURPOSE:** To investigate the prognostic value of intratumoral invariant natural killer T (iNKT) cells and interferon-gamma (IFN-gamma) in hepatocellular carcinoma (HCC) after curative resection. **EXPERIMENTAL DESIGN:** Expression of TRAV10, encoding the Valpha24 domain of iNKT cells, and IFN-gamma mRNA were assessed by quantitative real-time polymerase chain reaction in tumor from 224 HCC patients undergoing curative resection. The prognostic value of these two and other clinicopathologic factors was evaluated. **RESULTS:** Either intratumoral iNKT cells and IFN-gamma alone or their combination was an independent prognostic factor for OS (P = 0.001) and RFS (P = 0.001) by multivariate Cox proportional hazards analysis. Patients with concurrent low levels of iNKT cells and IFN-gamma had a hazard ratio (HR) of 2.784 for OS and 2.673 for RFS. The areas under the curve of iNKT cells, IFN-gamma and their combination were 0.618 vs 0.608 vs 0.654 for death and 0.591 vs 0.604 vs 0.633 for recurrence respectively by receiver operating characteristic curve analysis. The prognosis was the worst for HCC patients with concurrent low levels of iNKT cells and IFN-gamma, which might be related with more advanced pTNM stage and more vascular invasion. **CONCLUSIONS:** Combination of intratumoral iNKT cells and IFN-gamma is a promising independent predictor for recurrence and survival in HCC, which has a better power to predict HCC patients' outcome compared with intratumoral iNKT cells or IFN-gamma alone.

[935]

TÍTULO / TITLE: - Small molecule ErbB inhibitors decrease proliferative signaling and promote apoptosis in Philadelphia chromosome-positive acute lymphoblastic leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1371/journal.pone.0070608)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 1;8(8):e70608. doi: 10.1371/journal.pone.0070608. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070608](https://doi.org/10.1371/journal.pone.0070608)

AUTORES / AUTHORS: - Irwin ME; Nelson LD; Santiago-O'Farrill JM; Knouse PD; Miller CP; Palla SL; Siwak DR; Mills GB; Estrov Z; Li S; Kornblau SM; Hughes DP; Chandra J

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA.

RESUMEN / SUMMARY: - The presence of the Philadelphia chromosome in patients with acute lymphoblastic leukemia (Ph(+))ALL is a negative prognostic indicator. Tyrosine kinase inhibitors (TKI) that target BCR/ABL, such as imatinib, have improved treatment of Ph(+))ALL and are generally incorporated into induction regimens. This approach has improved clinical responses, but molecular remissions are seen in less than 50% of patients leaving few treatment options in the event of relapse. Thus, identification of additional targets for therapeutic intervention has potential to improve outcomes for Ph+ALL. The human epidermal growth factor receptor 2 (ErbB2) is expressed in ~30% of B-ALLs, and numerous small molecule inhibitors are available to prevent its activation. We analyzed a cohort of 129 ALL patient samples using reverse phase protein array (RPPA) with ErbB2 and phospho-ErbB2 antibodies and found that activity of ErbB2 was elevated in 56% of Ph(+))ALL as compared to just 4.8% of Ph(-))ALL. In two human Ph+ALL cell lines, inhibition of ErbB kinase activity with canertinib resulted in a dose-dependent decrease in the phosphorylation of an ErbB kinase signaling target p70S6-kinase T389 (by 60% in Z119 and 39% in Z181 cells at 3 microM). Downstream, phosphorylation of S6-kinase was also diminished in both cell lines in a dose-dependent manner (by 91% in both cell lines at 3 microM). Canertinib treatment increased expression of the pro-apoptotic protein Bim by as much as 144% in Z119 cells and 49% in Z181 cells, and further produced caspase-3 activation and consequent apoptotic cell death. Both canertinib and the FDA-approved ErbB1/2-directed TKI lapatinib abrogated proliferation and increased sensitivity to BCR/ABL-directed TKIs at clinically relevant doses. Our results suggest that ErbB signaling is an additional molecular target in Ph(+))ALL and encourage the development of clinical strategies combining ErbB and BCR/ABL kinase inhibitors for this subset of ALL patients.

[936]

TÍTULO / TITLE: - Prediction and Analysis of Retinoblastoma Related Genes through Gene Ontology and KEGG.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:304029. doi: 10.1155/2013/304029.

Epub 2013 Aug 13.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/304029](#)

AUTORES / AUTHORS: - Li Z; Li BQ; Jiang M; Chen L; Zhang J; Liu L; Huang T

INSTITUCIÓN / INSTITUTION: - Department of Ophthalmology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China.

RESUMEN / SUMMARY: - One of the most important and challenging problems in biomedicine is how to predict the cancer related genes. Retinoblastoma (RB) is the most common primary intraocular malignancy usually occurring in childhood. Early detection of RB could reduce the morbidity and promote the probability of disease-free survival. Therefore, it is of great importance to identify RB genes. In this study, we developed a computational method to predict RB related genes based on Dagging,

with the maximum relevance minimum redundancy (mRMR) method followed by incremental feature selection (IFS). 119 RB genes were compiled from two previous RB related studies, while 5,500 non-RB genes were randomly selected from Ensemble genes. Ten datasets were constructed based on all these RB and non-RB genes. Each gene was encoded with a 13,126-dimensional vector including 12,887 Gene Ontology enrichment scores and 239 KEGG enrichment scores. Finally, an optimal feature set including 1061 GO terms and 8 KEGG pathways was obtained. Analysis showed that these features were closely related to RB. It is anticipated that the method can be applied to predict the other cancer related genes as well.

[937]

TÍTULO / TITLE: - Overexpression of transglutaminase 4 and prostate cancer progression: a potential predictor of less favourable outcomes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian J Androl. 2013 Aug 26. doi: 10.1038/aja.2013.79.

●● [Enlace al texto completo \(gratis o de pago\) 1038/aja.2013.79](#)

AUTORES / AUTHORS: - Cao Z; Wang Y; Liu ZY; Zhang ZS; Ren SC; Yu YW; Qiao M; Zhai BB; Sun YH

INSTITUCIÓN / INSTITUTION: - Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China.

RESUMEN / SUMMARY: - Transglutaminase 4 has been shown to enhance various biological properties of prostate cancer cells, e.g., cell-matrix adhesion, invasiveness and the epithelial-mesenchymal transition. The objectives of this study were to investigate the associations between transglutaminase 4 expression and the established features and biochemical recurrence of prostate cancer. Transglutaminase 4 immunostaining was performed on a tissue microarray. The expression of transglutaminase 4 was evaluated by a scoring method based on the intensity and extent of staining. The clinical and pathological information was obtained through a review of medical records. Follow-up data were obtained by consulting the hospital medical records and the prostate cancer database of our department and by contacting patients or family members. We then compared the transglutaminase 4 expression levels between the prostate cancer tissues and the paracarcinoma tissues and evaluated the correlation of transglutaminase 4 expression with the clinical parameters and biochemical recurrence of prostate cancer. Our results indicated that the transglutaminase 4 staining was significantly higher in tumour tissue than in paracarcinoma tissue ($P < 0.001$) and was positively associated with higher Gleason score ($P < 0.001$) and higher prostate-specific antigen level ($P = 0.005$). Patients with transglutaminase 4 overexpression experienced shorter biochemical recurrence-free survival after surgery ($P = 0.042$) in the univariate analysis but not in the multivariate analysis ($P = 0.139$), which indicated that transglutaminase 4 may serve as a potential

predictor of biochemical recurrence of prostate cancer. Asian Journal of Andrology advance online publication, 26 August 2013; doi:10.1038/aja.2013.79.

[938]

TÍTULO / TITLE: - Hsp60 chaperonin acts as barrier to pharmacologically induced oxidative stress mediated apoptosis in tumor cells with differential stress response.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Drug Target Insights. 2013 Sep 1;7:35-51. doi: 10.4137/DTI.S12513.

●● Enlace al texto completo (gratis o de pago) [4137/DTI.S12513](#)

AUTORES / AUTHORS: - Sarangi U; Singh MK; Abhijnya KV; Reddy LP; Prasad BS; Pitke VV; Paithankar K; Sreedhar AS

INSTITUCIÓN / INSTITUTION: - CSIR-Centre for Cellular and Molecular Biology, Uppal Road, Hyderabad 500007, Andhra Pradesh, India.

RESUMEN / SUMMARY: - Mitochondrial functions play a central role in energy metabolism and provide survival fitness to both normal and tumor cells. Mitochondrial chaperonin Hsp60 is involved in both pro- and anti-apoptotic functions, but how Hsp60 senses the mitochondria selective oxidative stress response is unknown. In this study, by using rotenone, an irreversible inhibitor of oxidative phosphorylation against IMR-32 and BC-8 tumor cells containing differential heat shock transcriptional machinery, we studied whether the oxidative stress response is related to Hsp60. The accelerated cytotoxicity in response to rotenone has been correlated with enhanced production of O₂ (*-), H₂O₂, reactive oxygen species, and Hsp60 translocation from the mitochondria to the cytoplasm. The inability of cells to resist oxidative stress mediated Hsp60 translocation appeared to depend on mitochondrial oxyradical scavenging system and Bax translocation. A delayed oxidative stress response in hsp60 shRNA-treated cells was found to be due to increased mitochondrial translocation of Hsp60 on shRNA pre-sensitization. Overexpression of Hsp60 failed to protect cells from oxidative stress due to a lack of its mitochondrial retention upon post-rotenone treatment. These results also revealed that Hsp60 mitochondrial localization is indispensable for decreasing O₂ (*-) levels, but not H₂O₂ and ROS levels. However, cycloheximide treatment alone induced Hsp60 translocation, while rotenone combination delayed this translocation. In contrast to oxidative stress, MG132 and 17AAG treatments showed mitochondrial retention of Hsp60; however, MG132 combination either with hsp60 shRNA or 17AAG induced its translocation. Additionally, overexpression of Huntingtin gene also resulted in Hsp60 mitochondrial accumulation. We suggest that Hsp60 may act as a barrier to pharmacological targeting of mitochondria.

[939]

TÍTULO / TITLE: - Joint pain severity predicts premature discontinuation of aromatase inhibitors in breast cancer survivors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 3;13(1):401.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-401](#)

AUTORES / AUTHORS: - Chim K; Xie SX; Stricker CT; Li QS; Gross R; Farrar JT; Demichele A; Mao JJ

RESUMEN / SUMMARY: - BACKGROUND: Premature discontinuation of aromatase inhibitors (AIs) in breast cancer survivors compromises treatment outcomes. We aimed to evaluate whether patient-reported joint pain predicts premature discontinuation of AIs. METHODS: We conducted a retrospective cohort study of postmenopausal women with breast cancer on AIs who had completed a survey about their symptom experience on AIs with specific measurements of joint pain. The primary outcome was premature discontinuation of AIs, defined as stopping the medication prior to the end of prescribed therapy. Multivariate Cox regression modeling was used to identify predictors of premature discontinuation. RESULTS: Among 437 patients who met eligibility criteria, 47 (11%) prematurely discontinued AIs an average of 29 months after initiation of therapy. In multivariate analyses, patient-reported worst joint pain score of 4 or greater on the Brief Pain Inventory (BPI) (Hazard Ratio [HR] 2.09, 95% Confidence Interval [CI] 1.14-3.80, P = .016) and prior use of tamoxifen (HR 2.01, 95% CI 1.09-3.70, P = .026) were significant predictors of premature discontinuation of AIs. The most common reason for premature discontinuation was joint pain (57%) followed by other therapy-related side effects (30%). While providers documented joint pain in charts for 82% of patients with clinically important pain, no quantitative pain assessments were noted, and only 43% provided any plan for pain evaluation or management. CONCLUSION: Worst joint pain of 4 or greater on the BPI predicts premature discontinuation of AI therapy. Clinicians should monitor pain severity with quantitative assessments and provide timely management to promote optimal adherence to AIs.

[940]

TÍTULO / TITLE: - Moringa Oleifera aqueous leaf extract down-regulates nuclear factor-kappaB and increases cytotoxic effect of chemotherapy in pancreatic cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Aug 19;13:212. doi: 10.1186/1472-6882-13-212.

●● Enlace al texto completo (gratis o de pago) [1186/1472-6882-13-212](#)

AUTORES / AUTHORS: - Berkovich L; Earon G; Ron I; Rimmon A; Vexler A; Lev-Ari S
INSTITUCIÓN / INSTITUTION: - Laboratory of Herbal Medicine and Cancer Research, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel. Shaharl@tasmc.health.gov.il.

RESUMEN / SUMMARY: - BACKGROUND: Fewer than 6% patients with adenocarcinoma of the pancreas live up to five years after diagnosis. Chemotherapy is currently the standard treatment, however, these tumors often develop drug resistance over time.

Agents for increasing the cytotoxic effects of chemotherapy or reducing the cancer cells' chemo-resistance to the drugs are required to improve treatment outcome. Nuclear factor kappa B (NF- κ B), a pro-inflammatory transcription factor, reportedly plays a significant role in the resistance of pancreatic cancer cells to apoptosis-based chemotherapy. This study investigated the effect of aqueous Moringa Oleifera leaf extract on cultured human pancreatic cancer cells - Panc-1, p34, and COLO 357, and whether it can potentiates the effect of cisplatin chemotherapy on these cells. METHODS: The effect of Moringa Oleifera leaf extract alone and in combination with cisplatin on the survival of cultured human pancreatic cancer cells was evaluated by XTT-based colorimetric assay. The distribution of Panc-1 cells in the cell cycle following treatment with Moringa leaf extract was evaluated by flow cytometry, and evaluations of protein levels were via immunoblotting. Data of cell survival following combined treatments were analyzed with Calcosyn software. RESULTS: Moringa Oleifera leaf extract inhibited the growth of all pancreatic cell lines tested. This effect was significant in all cells following exposure to ≥ 0.75 mg/ml of the extract. Exposure of Panc-1 cells to Moringa leaf extract induced an elevation in the sub-G1 cell population of the cell-cycle, and reduced the expression of p65, p-I κ B α and I κ B α proteins in crude cell extracts. Lastly, Moringa Oleifera leaf extract synergistically enhanced the cytotoxic effect of cisplatin on Panc-1 cells. CONCLUSION: Moringa Oleifera leaf extract inhibits the growth of pancreatic cancer cells, the cells NF- κ B signaling pathway, and increases the efficacy of chemotherapy in human pancreatic cancer cells.

[941]

TÍTULO / TITLE: - From Determinants of RUNX1/ETO Tetramerization to Small-Molecule Protein-Protein Interaction Inhibitors Targeting Acute Myeloid Leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Chem Inf Model. 2013 Sep 12.

●● [Enlace al texto completo \(gratis o de pago\) 1021/ci400332e](#)

AUTORES / AUTHORS: - Metz A; Schanda J; Grez M; Wichmann C; Gohlke H

INSTITUCIÓN / INSTITUTION: - Institute for Pharmaceutical and Medicinal Chemistry, Department of Mathematics and Natural Sciences, Heinrich-Heine-University, Universitätsstr. 1, 40225 Dusseldorf, Germany.

RESUMEN / SUMMARY: - We identified the first small-molecule protein-protein interaction inhibitors of RUNX1/ETO tetramerization applying structure-based virtual screening guided by predicted hot spots and pockets in the interface. A 3D similarity screening revealed specific hot spot mimetics, one of which prevents the proliferation of RUNX1/ETO-dependent SKNO-1 cells at low micromolar concentration. Using solely a protein-protein complex structure to start with, this strategy can be the first step in any comparable structure-based endeavor to identify protein-protein interaction inhibitors.

[942]

TÍTULO / TITLE: - Prediction of glycan motifs using quantitative analysis of multi-lectin binding: Motifs on MUC1 produced by cultured pancreatic cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Proteomics Clin Appl. 2013 Aug 19. doi: 10.1002/prca.201300069.

●● Enlace al texto completo (gratis o de pago) [1002/prca.201300069](#)

AUTORES / AUTHORS: - McCarter C; Kletter D; Tang H; Partyka K; Ma Y; Singh S; Yadav J; Bern M; Haab BB

INSTITUCIÓN / INSTITUTION: - Van Andel Research Institute, Grand Rapids, MI, USA.

RESUMEN / SUMMARY: - PURPOSE: Lectins are valuable tools for detecting specific glycans in biological samples, but the interpretation of the measurements can be ambiguous due to the complexities of lectin specificities. Here, we present an approach to improve the accuracy of interpretation by converting lectin measurements into quantitative predictions of the presence of various glycan motifs. EXPERIMENTAL DESIGN: The conversion relies on a database of analyzed glycan array data that provides information on the specificities of the lectins for each of the motifs. We tested the method using measurements of lectin binding to glycans on glycan arrays and then applied the method to predicting motifs on the protein mucin 1 (MUC1) expressed in eight different pancreatic cancer cell lines. RESULTS: The combined measurements from several lectins were more accurate than individual measurements for predicting the presence or absence of motifs on arrayed glycans. The analysis of MUC1 revealed that each cell line expressed a unique pattern of glycoforms, and that the glycoforms significantly differed between MUC1 collected from conditioned media and MUC1 collected from cell lysates. CONCLUSIONS AND CLINICAL RELEVANCE: This new method could provide more accurate analyses of glycans in biological sample and make the use of lectins more practical and effective for a broad range of researchers.

[943]

TÍTULO / TITLE: - Effect of folic Acid and vitamin B12 on pemetrexed antifolate chemotherapy in nutrient lung cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:389046. doi: 10.1155/2013/389046. Epub 2013 Jul 31.

●● Enlace al texto completo (gratis o de pago) [1155/2013/389046](#)

AUTORES / AUTHORS: - Yang TY; Chang GC; Hsu SL; Huang YR; Chiu LY; Sheu GT

INSTITUCIÓN / INSTITUTION: - Institute of Medicine, Chung Shan Medical University, No. 110, Sec 1, Jianguo N. Road, Taichung 402, Taiwan ; Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, No. 160, Sec 3, Chung-Kang, Taichung 407, Taiwan.

RESUMEN / SUMMARY: - Pemetrexed (MTA) is a multitargeted antifolate drug approved for lung cancer therapy. Clinically, supplementation with high doses of folic acid (FA) and vitamin B12 (VB12) lowers MTA cytotoxicities. An antagonistic effect of FA/VB12 on MTA efficacy has been proposed. However, patients who receive FA/VB12 show better tolerance to MTA with improved survival. The aims of this study are to investigate the modulation of FA and VB12 on MTA drug efficacy in human nonsmall cell lung cancer (NSCLC) cell lines. The sensitivities of cells, apoptosis, and MTA-regulated proteins were characterized to determine the possible effects of high doses of FA and VB12 on MTA efficacy. MTA has the lowest efficacy under 10% serum conditions. However, supplementation with FA and VB12 individually and additively reversed the insensitivity of NSCLC cells to MTA treatment with 10% serum. The enhanced sensitivities of cells following FA/VB12 treatment were correlated with increasing apoptosis and were specific to MTA but not to 5-fluorouracil (5-FU). Enhanced sensitivity was also associated with p21(WAF1/Cip1) expression level. Our results revealed no antagonistic effect of high doses of FA/VB12 on MTA efficacy in cancer cells grown in nutrient medium. Furthermore, these data may partially explain why supplementation of FA and VB12 resulted in better survival in MTA-treated patients.

[944]

TÍTULO / TITLE: - Molecular crosstalk between apoptosis and autophagy induced by a novel 2-methoxyestradiol analogue in cervical adenocarcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Aug 27;13(1):87.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1475-2867-13-87](#)

AUTORES / AUTHORS: - Theron AE; Nolte EM; Lafanechere L; Joubert AM

RESUMEN / SUMMARY: - BACKGROUND: 2-Methoxyestradiol has been shown to induce both autophagy and apoptosis in various carcinogenic cell lines. Although a promising anti-cancer agent, it has poor bioavailability and rapid in vivo metabolism which decreases its efficiency. In order to improve 2-methoxyestradiol's anti-proliferative properties, a novel 2-methoxyestradiol analogue, 2-ethyl-3-O-sulphamoyl-estra-1,3,5(10)16-tetraene (ESE-16), was previously in silico-designed in our laboratory. This study investigated ESE-16 for its anti-proliferative potential on a cervical adenocarcinoma cell (HeLa) cell line. Additionally, the possible intracellular crosstalk mechanisms between the two types of cell death were investigated. Methods and results: HeLa cells exposed to 0.5 μM ESE-16 for 24 hours showed morphological evidence of both apoptotic and autophagic death pathways as assessed by polarization-optical transmitted light differential interference contrast microscopy, fluorescent microscopy and transmission electron microscopy. Flow cytometric cyclin B1 quantification revealed induction of programmed cell death after halting cell cycle progression in metaphase. Confocal microscopy demonstrated that ESE-16 caused microtubule

fragmentation. Flow cytometric analysis of cell cycle progression and phosphatidylserine flip determination confirmed induction of apoptosis. Moreover, an increase in aggresome formation and microtubule-associated protein light chain, LC3, was demonstrated indicative of autophagy. Both caspase 8 and 3 were upregulated in a spectrophotometric analysis, indicating the involvement of the extrinsic pathway of apoptotic induction. CONCLUSIONS: We conclude that the novel in silico-designed compound, ESE-16, exerts its anti-proliferative effect on the tumorigenic human epithelial cervical (HeLa) cells by sequentially targeting microtubule integrity, resulting in a metaphase block, causing induction of both autophagic and apoptotic cell death via a crosstalk mechanism that involves the extrinsic pathway. Future investigations will expand on signal transduction pathways involved in both apoptosis and autophagy for assessment of ESE-16 effects on microtubule dynamic instability parameters.

[945]

TÍTULO / TITLE: - ABT-737, a small molecule Bcl-2/Bcl-xL antagonist, increases antimetastatic-mediated apoptosis in human prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PeerJ. 2013 Sep 12;1:e144. doi: 10.7717/peerj.144.

●● [Enlace al texto completo \(gratis o de pago\) 7717/peerj.144](#)

AUTORES / AUTHORS: - Parrondo R; de Las Pozas A; Reiner T; Perez-Stable C

INSTITUCIÓN / INSTITUTION: - Geriatric Research, Education, and Clinical Center and Research Service, Bruce W. Carter Veterans Affairs Medical Center, Miami, FL, USA.

RESUMEN / SUMMARY: - Castration-resistant prostate cancer (CRPC) expresses high levels of the anti-apoptotic proteins Bcl-2, Bcl-xL and Mcl-1, resulting in resistance to apoptosis and association with poor prognosis. Docetaxel, an antimetastatic drug that is the first-line treatment strategy for CRPC, is known to provide a small survival benefit. However, docetaxel chemotherapy alone is not enough to counteract the high levels of Bcl-2/Bcl-xL/Mcl-1 present in CRPC. ABT-737 is a small molecule that binds to Bcl-2/Bcl-xL (but not Mcl-1) with high affinity and disrupts their interaction with pro-apoptotic Bax/Bak, thus enhancing apoptosis. Our results indicate that ABT-737 can sensitize androgen-dependent LNCaP and CRPC PC3 cells to docetaxel- and to the novel antimetastatic ENMD-1198-mediated caspase-dependent apoptosis. CRPC DU145 cells, however, are more resistant to ABT-737 because they are Bax null and not because they express the highest levels of anti-apoptotic Mcl-1 (associated with ABT-737 resistance). Knockdown of Bax or Bak in LNCaP indicates that ABT-737-induced antimetastatic enhancement of apoptosis is more dependent on the levels of Bax than Bak. Furthermore, we find that the ability of docetaxel to increase cyclin B1/Cdk1-mediated phosphorylation of Bcl-2/Bcl-xL and decrease Mcl-1 is required for ABT-737 to enhance apoptosis in PC3 cells, as determined by addition of Cdk1 inhibitor purvalanol A and expression of shRNA specific for cyclin B1. Overall, our data suggests

that the high levels of anti-apoptotic proteins in Bax-expressing CRPC cells can be overcome by targeting Bcl-2/Bcl-xL with ABT-737 and Mcl-1 with antimitotics.

[946]

TÍTULO / TITLE: - CTA095, a Novel Etk and Src Dual Inhibitor, Induces Apoptosis in Prostate Cancer Cells and Overcomes Resistance to Src Inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e70910. doi: 10.1371/journal.pone.0070910.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070910](#)

AUTORES / AUTHORS: - Guo W; Liu R; Bhardwaj G; Ma AH; Changou C; Yang JC; Li Y; Feng C; Luo Y; Mazloom A; Sanchez E; Wang Y; Huang W; Patterson R; Evans CP; Lam KS; Kung HJ

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Medicine, University of California Davis, Sacramento, California, United States of America.

[947]

TÍTULO / TITLE: - Ets-2 Regulates Cell Apoptosis via the Akt Pathway, through the Regulation of Urothelial Cancer Associated 1, a Long Non-Coding RNA, in Bladder Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 12;8(9):e73920. doi: 10.1371/journal.pone.0073920.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073920](#)

AUTORES / AUTHORS: - Wu W; Zhang S; Li X; Xue M; Cao S; Chen W

INSTITUCIÓN / INSTITUTION: - Clinical Laboratory, the First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, China.

RESUMEN / SUMMARY: - The majority of the human genome is transcribed and generates non-coding RNAs (ncRNAs) that fail to encode protein information. Long non-coding RNAs (lncRNAs) are emerging as a novel class of ncRNAs, but our knowledge about these ncRNAs is limited. Previously, our laboratory has identified that a lncRNA, Urothelial cancer associated 1 (UCA1), played an important role in bladder cancer. Despite the recent interest in UCA1 as a diagnostic marker for bladder cancer, little is known about its transcriptional regulation. To elucidate the regulation of UCA1 gene expression, we have characterized the human UCA1 gene promoter. A 2.0-kb fragment of its 5' flanking region was cloned into a luciferase reporter vector. Deletion and mutation analysis suggested that an Ets-2 binding site was critical for UCA1 gene promoter activity. Further analysis of this site by gel shifting, chromatin immune precipitation (ChIP), and co-transfection experiments showed that transcription factor Ets-2 directly bound to the UCA1 promoter region and stimulated UCA1 promoter activity in bladder cancer cells. Taking into account the anti-apoptosis function of Ets-2, our data suggested that Ets-2 regulates apoptosis process by regulating the expression

of UCA1, moreover UCA1 may be involved in the activation of Akt signaling pathway by Ets-2 in bladder cancer cells.

[948]

TÍTULO / TITLE: - Correction: Functional disruption of macrophage migration inhibitory factor (MIF) suppresses proliferation of human h460 lung cancer cells by caspase-dependent apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Aug 20;13(1):84.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-84](#)

AUTORES / AUTHORS: - Guo Y; Hou J; Luo Y; Wang D

RESUMEN / SUMMARY: - After publication of the original article [1] it came to the authors attention that an incomplete version of figure three was published with the article. The complete figure and new figure legend are presented in this correction article.

[949]

TÍTULO / TITLE: - The Synthetic Compound Norcantharidin Induced Apoptosis in Mantle Cell Lymphoma In Vivo and In Vitro through the PI3K-Akt-NF- kappa B Signaling Pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:461487. doi: 10.1155/2013/461487. Epub 2013 Jul 7.

●● Enlace al texto completo (gratis o de pago) [1155/2013/461487](#)

AUTORES / AUTHORS: - Lv H; Du H; Fang J; Song X; Zhang J

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Third Hospital of Hebei Medical University, 139 Ziqiang Road, Shijiazhuang 050051, China.

RESUMEN / SUMMARY: - This study aimed to elucidate the antitumor activity of norcantharidin (NCTD) against human mantle cell lymphoma (MCL). Cell proliferation and apoptosis were examined by MTS and flow cytometry. Caspase-3, -8, and -9 activities were detected with a colorimetric caspase protease assay. Apoptotic proteins-including PARP, cyclin D1, Bcl-2 family proteins, XIAP, and cIAP I-were studied by western blot. The phosphoinositide 3 kinase (PI3K) inhibitor LY294002 was used to investigate the involvement of the PI3K/Akt signaling pathway. In vivo studies were performed using Z138 cell xenografts in nude mice. NCTD inhibited proliferation and induced apoptosis of Z138 and Mino cells, both in vitro and in vivo. PI3Kp110 alpha and p-Akt expressions were downregulated by NCTD treatment. NCTD downregulated NF- kappa B activity by preventing NF- kappa B phosphorylation and nuclear translocation. This effect was correlated with the suppression of NF- kappa B-regulated gene products, such as cyclin D1, BAX, survivin, Bcl-2, XIAP, and cIAP. This phenomenon was blocked by the PI3K inhibitor LY294002. Our results demonstrated that NCTD can induce growth arrest and apoptosis in MCL cells and that the

mechanism may involve the PI3K/Akt/NF- kappa B signaling pathway. NCTD may have therapeutic and/or adjuvant therapeutic applications in the treatment of MCL.

[950]

TÍTULO / TITLE: - Daunorubicin, cytarabine, and cladribine regimen plus radiotherapy and donor lymphocyte infusion for extramedullary relapse of acute myeloid leukemia after hematopoietic stem cell transplantation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Case Rep Hematol. 2013;2013:258028. doi: 10.1155/2013/258028. Epub 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [1155/2013/258028](#)

AUTORES / AUTHORS: - Sanna M; Caocci G; Vacca A; Piras E; Orru F; La Nasa G

INSTITUCIÓN / INSTITUTION: - Hematology Unit and Bone Marrow Transplantation Center, "R. Binaghi" Hospital, Via Is Guadazzonis 3, 09126 Cagliari, Italy.

RESUMEN / SUMMARY: - Myeloid sarcoma is a rare tumor consisting of myeloid blasts that involve anatomic sites outside the bone marrow. Fatal prognosis is inevitable in patients with extramedullary relapse after hematopoietic stem cell transplantation (HSCT), and no standard treatments are available yet. We report the first case of extramedullary relapse after HSCT treated with a combination of daunorubicin, cytarabine, and cladribine (DAC) regimen plus radiotherapy and donor lymphocyte infusion (DLI). This treatment induced a new and durable remission in our patient. The favorable toxicity profile and the reduced cost make this combination worthy of further investigations.

[951]

TÍTULO / TITLE: - Gene Expression Network Analysis of ETV1 Reveals KCTD10 as a Novel Prognostic Biomarker in Gastrointestinal Stromal Tumor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 19;8(8):e73896. doi: 10.1371/journal.pone.0073896.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073896](#)

AUTORES / AUTHORS: - Kubota D; Yoshida A; Tsuda H; Suehara Y; Okubo T; Saito T; Orita H; Sato K; Taguchi T; Yao T; Kaneko K; Katai H; Kawai A; Kondo T

INSTITUCIÓN / INSTITUTION: - Division of Pharmacoproteomics, National Cancer Centre Research Institute, Tokyo, Japan ; Department of Orthopedic Surgery, Juntendo University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Prognostic biomarkers are required for risk stratification therapy in the patients with gastrointestinal stromal tumor (GIST). In this study, we aimed to identify prognostic biomarkers in GIST. We assessed the prognostic value of E twenty-six variant 1 (ETV1), a recently identified transcription factor unique to GIST. We also examined the clinical utility and functions of its

downstream gene, potassium channel tetramerization domain containing protein 10 (KCTD10). METHODS: The levels of ETV1 and KCTD10 were evaluated immunohistochemically in 112 patients with GIST treated at two hospitals. The functional properties of KCTD10 were examined by gene silencing assay in cultured GIST cells. RESULTS: Immunohistochemistry revealed that ETV1 expression in GIST had no prognostic significance. In contrast, the disease-free survival rate was 88.5% in patients with KCTD10-positive tumors and 55.8% in those with KCTD10-negative tumors ($p < 0.0001$). KCTD10 was an independent prognostic factor ($p < 0.05$). In the low-risk classification group, KCTD10 was significantly associated with favorable prognosis ($p = 0.0008$). Gene silencing of KCTD10 increased cell proliferation and invasion, suggesting that KCTD10 has a tumor-suppressive function. CONCLUSIONS: The GIST-specific transcription factor ETV1 may have no prognostic potential, whereas its downstream gene KCTD10 is associated with a favorable prognosis. Our study indicated the novel prognostic utility of KCTD10 in GIST, and suggested its tumor-suppressive effects on GIST cells. Further validation studies of KCTD10 for clinical applications, and functional verification of KCTD10 for better understanding of molecular basis of malignant phenotypes are worth challenging in GIST.

[952]

TÍTULO / TITLE: - Tumor necrosis factor-alpha attenuates starvation-induced apoptosis through upregulation of ferritin heavy chain in hepatocellular carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 25;13(1):438.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-438](#)

AUTORES / AUTHORS: - Kou X; Jing Y; Deng W; Sun K; Han Z; Ye F; Yu G; Fan Q; Gao L; Zhao Q; Zhao X; Li R; Wei L; Wu M

RESUMEN / SUMMARY: - BACKGROUND: Tumor microenvironment is characteristic of inflammation, ischemia and starvation of nutrient. TNF-alpha, which is an extraordinarily pleiotropic cytokine, could be an endogenous tumor promoter in some tumor types. The basic objective of this study was to investigate the effects of TNF-alpha on the cell viability and apoptosis of hepatocellular carcinoma cells under serum starvation, and to identify the molecular mechanisms involved. METHODS: For this purpose, five different concentrations of TNF-alpha and two different serum settings (serum-cultured and serum-deprived) were used to investigate the effects of TNF-alpha on the cell viability and apoptosis of Hep3B and SMMC-7721 cells. RESULTS: TNF-alpha (10 ng/ml) attenuated serum starvation-induced apoptosis of hepatocellular carcinoma cells, and autophagy conferred this process. BAY11-7082, a specific inhibitor of NF-kappaB, reversed the suppression of serum starvation-induced apoptosis by TNF-alpha. Moreover, TNF-alpha-induced NF-kappaB transactivation was suppressed by autophagy inhibitor 3-MA. In addition, TNF-alpha up-regulated Ferritin heavy chain (FHC) transiently by NF-kappaB activation and FHC levels were correlated with the

TNF-alpha-induced protection against serum starvation-mediated apoptosis of hepatocellular carcinoma cells. Furthermore, FHC-mediated inhibition of apoptosis depended on suppressing ROS accumulation. CONCLUSIONS: Our findings suggested that autophagy conferred the TNF-alpha protection against serum starvation-mediated apoptosis of hepatocellular carcinoma cells, the mechanism involved with the activation of the TNF-alpha/ NF-kappaB /FHC signaling pathway.

[953]

TÍTULO / TITLE: - BRAF(V600E) mutation is not a positive predictor for distant metastasis in sporadic papillary thyroid carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin Med J (Engl). 2013 Aug;126(16):3013-8.

AUTORES / AUTHORS: - Jing FJ; Liang J; Liang ZY; Meng C; Long W; Li XY; Lin YS

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Affiliated Hospital of Qingdao Medical College, Qingdao University, Qingdao, Shandong 266003, China.

RESUMEN / SUMMARY: - BACKGROUND: BRAF(V600E) mutation is correlated with local aggressive clinicopathological features in papillary thyroid carcinoma; yet the relationship between this genetic variation and distant papillary thyroid carcinoma metastasis was unclear. This study aimed to investigate whether BRAF(V600E) is predictive for distant metastasis in the Chinese population. METHODS: One hundred and seven patients with papillary thyroid carcinoma were enrolled in this study, including 43 patients with distant metastasis and 64 patients without. Quantitative real-time polymerase chain reaction was used to detect BRAF(V600E) mutation, while immunohistochemistry was performed to detect vascular endothelial growth factor (VEGF) expression. The associations between distant metastasis and BRAF(V600E) mutation, and VEGF expression as well as local clinicopathological factors were determined. RESULTS: A total of 28.6% of the patients in the distant metastasis group harbored BRAF(V600E) mutation, which was significantly lower than in the without distant metastasis group (68.8%, $P < 0.001$). BRAF(V600E) mutation was negatively correlated with positive VEGF expression ($P = 0.001$). Furthermore, 52.2% of the patients with distant metastasis exhibited VEGF expression, compared with 25.0% of those without. Higher levels of VEGF expression were also observed in the distant metastasis group. Tumor size, extra-thyroid invasion, and BRAF(V600E) mutation were independent predictors for distant metastasis according to multivariate analysis (odds ratios were 2.8, 12.4, and 0.3; 95% CI 1.483-5.334, and 2.950-52.407, 0.100-0.890; $P = 0.002$, 0.001 , and 0.030 , respectively). BRAF(V600E) mutation was negatively correlated with distant metastasis in adult subgroup analysis ($P = 0.005$) but was not an independent parameter. CONCLUSIONS: BRAF(V600E) mutation is predictive for distant metastasis in papillary thyroid carcinoma but not positively. VEGF may be involved in the pathogenesis of distant metastasis.

[954]

TÍTULO / TITLE: - miR-106^a-5p Inhibits the Proliferation and Migration of Astrocytoma Cells and Promotes Apoptosis by Targeting FASTK.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 27;8(8):e72390. doi: 10.1371/journal.pone.0072390.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072390](#)

AUTORES / AUTHORS: - Zhou G; Shao N; Xia X; Shi Y; Wang Q; Zhang Y; Wang R; Xue L; Wang S; Wu S; Peng Y; Yang Y

INSTITUCIÓN / INSTITUTION: - Modern Medical Research Center, Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, China.

RESUMEN / SUMMARY: - Astrocytomas are common malignant intracranial tumors that comprise the majority of adult primary central nervous system tumors. MicroRNAs (miRNAs) are small, non-coding RNAs (20-24 nucleotides) that post-transcriptionally modulate gene expression by negatively regulating the stability or translational efficiency of their target mRNAs. In our previous studies, we found that the downregulation of miR-106^a-5p in astrocytomas is associated with poor prognosis. However, its specific gene target(s) and underlying functional mechanism(s) in astrocytomas remain unclear. In this study, we used mRNA microarray experiments to measure global mRNA expression in the presence of increased or decreased miR-106^a-5p levels. We then performed bioinformatics analysis based on multiple target prediction algorithms to obtain candidate target genes that were further validated by computational predictions, western blot analysis, quantitative real-time PCR, and the luciferase reporter assay. Fas-activated serine/threonine kinase (FASTK) was identified as a direct target of miR-106^a-5p. In human astrocytomas, miR-106^a-5p is downregulated and negatively associated with clinical staging, whereas FASTK is upregulated and positively associated with advanced clinical stages, at both the protein and mRNA levels. Furthermore, Kaplan-Meier analysis revealed that the reduced expression of miR-106^a-5p or the increased expression of FASTK is significantly associated with poor survival outcome. These results further supported the finding that FASTK is a direct target gene of miR-106^a-5p. Next, we explored the function of miR-106^a-5p and FASTK during astrocytoma progression. Through gain-of-function and loss-of-function studies, we demonstrated that miR-106^a-5p can significantly inhibit cell proliferation and migration and can promote cell apoptosis in vitro. The knockdown of FASTK induced similar effects on astrocytoma cells as those induced by the overexpression of miR-106^a-5p. These observations suggest that miR-106^a-5p functions as a tumor suppressor during the development of astrocytomas by targeting FASTK.

[955]

TÍTULO / TITLE: - Selective GPER activation decreases proliferation and activates apoptosis in tumor Leydig cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 1;4:e747. doi: 10.1038/cddis.2013.275.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.275](#)

AUTORES / AUTHORS: - Chimento A; Casaburi I; Bartucci M; Patrizii M; Dattilo R; Avena P; Ando S; Pezzi V; Sirianni R

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Arcavacata di Rende, Cosenza, Italy.

RESUMEN / SUMMARY: - We have previously shown that estrogens binding to estrogen receptor (ER) alpha increase proliferation of Leydig tumor cells. Estrogens can also bind to G protein-coupled ER (GPER) and activation of this receptor can either increase or decrease cell proliferation of several tumor types. The aim of this study was to investigate GPER expression in R2C rat tumor Leydig cells, evaluate effects of its activation on Leydig tumor cell proliferation and define the molecular mechanisms triggered in response to its activation. R2C cells express GPER and its activation, using the specific ligand G-1, is associated with decreased cell proliferation and initiation of apoptosis. Apoptosis after G-1 treatment was asserted by appearance of DNA condensation and fragmentation, decrease in Bcl-2 and increase in Bax expression, cytochrome c release, caspase and poly (ADP-ribose) polymerase-1 (PARP-1) activation. These effects were dependent on GPER activation because after silencing of the gene, using a specific small interfering RNA, cyt c release, PARP-1 activation and decrease in cell proliferation were abrogated. These events required a rapid, however, sustained extracellular regulated kinase ½ activation. G-1 was able to decrease the growth of R2C xenograft tumors in CD1 nude mice while increasing the number of apoptotic cells. In addition, in vivo administration of G-1 to male CD1 mice did not cause any alteration in testicular morphology, while cisplatin, the cytotoxic drug currently used for the therapy of Leydig tumors, severely damaged testicular structure, an event associated with infertility in cisplatin-treated patients. These observations indicate that GPER targeting for the therapy of Leydig cell tumor may represent a good alternative to cisplatin to preserve fertility in Leydig tumor patients.

[956]

TÍTULO / TITLE: - MicroRNA-185 and 342 Inhibit Tumorigenicity and Induce Apoptosis through Blockade of the SREBP Metabolic Pathway in Prostate Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e70987. doi: 10.1371/journal.pone.0070987.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070987](#)

AUTORES / AUTHORS: - Li X; Chen YT; Josson S; Mukhopadhyay NK; Kim J; Freeman MR; Huang WC

INSTITUCIÓN / INSTITUTION: - Uro-Oncology Research Program, Department of Medicine, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, United States of America.

RESUMEN / SUMMARY: - MicroRNA (miRNA or miR) inhibition of oncogenic related pathways has been shown to be a promising therapeutic approach for cancer. Aberrant lipid and cholesterol metabolism is involved in prostate cancer development and progression to end-stage disease. We recently demonstrated that a key transcription factor for lipogenesis, sterol regulatory element-binding protein-1 (SREBP-1), induced fatty acid and lipid accumulation and androgen receptor (AR) transcriptional activity, and also promoted prostate cancer cell growth and castration resistance. SREBP-1 was overexpressed in human prostate cancer and castration-resistant patient specimens. These experimental and clinical results indicate that SREBP-1 is a potential oncogenic transcription factor in prostate cancer. In this study, we identified two miRNAs, miR-185 and 342, that control lipogenesis and cholesterologenesis in prostate cancer cells by inhibiting SREBP-1 and 2 expression and down-regulating their targeted genes, including fatty acid synthase (FASN) and 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR). Both miR-185 and 342 inhibited tumorigenicity, cell growth, migration and invasion in prostate cancer cell culture and xenograft models coincident with their blockade of lipogenesis and cholesterologenesis. Intrinsic miR-185 and 342 expression was significantly decreased in prostate cancer cells compared to non-cancerous epithelial cells. Restoration of miR-185 and 342 led to caspase-dependent apoptotic death in prostate cancer cells. The newly identified miRNAs, miR-185 and 342, represent a novel targeting mechanism for prostate cancer therapy.

[957]

TÍTULO / TITLE: - Circulating tumor cells and DNA as liquid biopsies.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genome Med. 2013 Aug 23;5(8):73.

●● [Enlace al texto completo \(gratis o de pago\) 1186/gm477](#)

AUTORES / AUTHORS: - Heitzer E; Auer M; Ulz P; Geigl JB; Speicher MR

INSTITUCIÓN / INSTITUTION: - Institute of Human Genetics, Medical University of Graz, Harrachgasse 21/8, A-8010 Graz, Austria. michael.speicher@medunigraz.at.

RESUMEN / SUMMARY: - For cancer patients, the current approach to prognosis relies on clinicopathological staging, but usually this provides little information about the individual response to treatment. Therefore, there is a tremendous need for protein and genetic biomarkers with predictive and prognostic information. As biomarkers are identified, the serial monitoring of tumor genotypes, which are instable and prone to changes under selection pressure, is becoming increasingly possible. To this end, circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) shed from primary and metastatic cancers may allow the non-invasive analysis of the evolution of tumor

genomes during treatment and disease progression through 'liquid biopsies'. Here we review recent progress in the identification of CTCs among thousands of other cells in the blood and new high-resolution approaches, including recent microfluidic platforms, for dissecting the genomes of CTCs and obtaining functional data. We also discuss new ctDNA-based approaches, which may become a powerful alternative to CTC analysis. Together, these approaches provide novel biological insights into the process of metastasis and may elucidate signaling pathways involved in cell invasiveness and metastatic competence. In medicine these liquid biopsies may emerge to be powerful predictive and prognostic biomarkers and could therefore be instrumental for areas such as precision or personalized medicine.

[958]

TÍTULO / TITLE: - Synthesis of a new bis(indolyl)methane that inhibits growth and induces apoptosis in human prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nat Prod Res. 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1080/14786419.2013.824440](https://doi.org/10.1080/14786419.2013.824440)

AUTORES / AUTHORS: - Marrelli M; Cachet X; Conforti F; Sirianni R; Chimento A; Pezzi V; Michel S; Statti GA; Menichini F

INSTITUCIÓN / INSTITUTION: - a Department of Pharmacy, Health and Nutritional Sciences , University of Calabria , via Pietro Bucci , I-87036 , Rende (CS) , Italy.

RESUMEN / SUMMARY: - The synthesis and the antiproliferative activity against the human breast MCF-7, SkBr3 and the prostate LNCaP cancer cell lines of a series of bis(indolyl)methane derivatives are reported. The synthesis of new compounds was first accomplished by the reaction of different indoles with trimethoxyacetophenone in the presence of catalytic amounts of hydrochloric acid. A second procedure involving the use of oxalic acid dihydrate [(CO₂H)₂.2H₂O] and N-cetyl-N,N,N-trimethylammonium bromide in water was carried out and led to better yields. Compound 5b significantly reduced LNCaP prostate cancer cell viability in a dose-dependent manner, with an IC₅₀ of 0.64 +/- 0.09 μM. To determine whether the growth inhibition was associated with the induction of apoptosis, treated cells were stained using DAPI. LNCaP cells treated with 1 μM of 5b showed the morphological changes characteristic of apoptosis after 24 h of incubation.

[959]

TÍTULO / TITLE: - Biomarkers of medullary thyroid cancer in the prediction of cure after thyroidectomy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Formos Med Assoc. 2013 Jul 29. pii: S0929-6646(13)00220-9. doi: 10.1016/j.jfma.2013.06.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.jfma.2013.06.016](https://doi.org/10.1016/j.jfma.2013.06.016)

AUTORES / AUTHORS: - Nien FJ; Chang TC

INSTITUCIÓN / INSTITUTION: - Division of Endocrinology and Metabolism, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

[960]

TÍTULO / TITLE: - Effect of DNA methylation inhibitor on RASSF1A genes expression in non-small cell lung cancer cell line A549 and A549DDP.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Sep 8;13(1):91.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-91](#)

AUTORES / AUTHORS: - Mengxi D; Qian W; Nan W; Xiaoguang X; Shijun L

RESUMEN / SUMMARY: - BACKGROUND: Ras association domain family 1^a gene (RASSF1A) is a candidate suppressor gene, Lack of RASSF1A expression was found in lung cancer. High DNA methylation at the promoter region is the main reason for inactivating RASSF1A transcription. METHODS: In this study, we examined RASSF1A's methylation status and its mRNA expression level between non-small cell lung cancer cell line A549 and anti-Cisplatin cell strain A549DDP, Furthermore, methylation of A549DDP was reversed by treatment of 5-Aza-2[prime] - deoxycytidine (5-Aza-cdR), a DNA methyltransferase inhibitor. RESULTS: We found that RASSF1A's methylation status and its mRNA expression were obvious differences between A549 and A549DDP. 5-Aza-CdR treatment remarkably reduced cell viability of A549DDP. Moreover, 5-Aza-CdR treatment induced A549DDP cell apoptosis in a dose dependent manner with declining cell percentage in S and G2/M stage, and increasing proportion in G0/G1 stage. Cell motility was blocked in G0/G1 stage. All of A549DDP cells showed unmethylated expression, its high methylation status was reversed in a dose-dependent manner within a certain range. CONCLUSIONS: The abnormal gene methylation status of RASSF1A is a molecular biomarker in lung cancer diagnosis, treatment and prognosis.

[961]

TÍTULO / TITLE: - Arsenic trioxide inhibits viability of pancreatic cancer stem cells in culture and in a xenograft model via binding to SHH-Gli.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Aug 19;6:1129-38. doi: 10.2147/OTT.S49148.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S49148](#)

AUTORES / AUTHORS: - Han JB; Sang F; Chang JJ; Hua YQ; Shi WD; Tang LH; Liu LM

INSTITUCIÓN / INSTITUTION: - Department of integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China ; Department of

Oncology, Shanghai Medical College, Fudan University, Shanghai, People's Republic of China.

RESUMEN / SUMMARY: - OBJECTIVE: Overexpression of the sonic hedgehog (SHH) signaling pathway is an essential characteristic of pancreatic cancer stem cells (PCSCs) and arsenic trioxide (ATO) is described as a SHH inhibitor. This study evaluates whether ATO has the potential to inhibit viability of PCSCs via binding to SHH-Gli proteins. METHODS: Cell counting kit-8 and flow cytometry were used for analyzing apoptosis in cells in vitro. The animal model was an athymic nude mouse model bearing subcutaneous xenografts of SW1990 pancreatic cancer cells. The terminal deoxynucleotidyl transferase dUTP nick end labeling assay and immunohistochemistry were used for tumor tissue analysis. The interaction between Gli1 and ATO was examined by a confocal system and an ultraviolet absorption spectrum assay. RESULTS: ATO induced apoptosis in pancreatic cancer cells, especially CD24(+)CD44(+) cells in vitro. Combination treatment of ATO and low dose gemcitabine inhibited tumor growth by 60.9% (P = 0.004), and decreased the expression of CD24, CD44, and aldehyde dehydrogenase 1 family, member A1 significantly in vivo. ATO changed the structure of the recombinant Gli1 zinc finger peptides in a cell-free condition and the binding action of ATO to recombinant Gli1 was observed in cultured pancreatic cancer cells. CONCLUSION: ATO may have the potential to inhibit viability of PCSCs via binding to SHH-Gli proteins in vitro and in vivo.

[962]

TÍTULO / TITLE: - Phenothiazine Inhibitors of TLKs Affect Double-Strand Break Repair and DNA Damage Response Recovery and Potentiate Tumor Killing with Radiomimetic Therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genes Cancer. 2013 Jan;4(1-2):39-53. doi: 10.1177/1947601913479020.

- Enlace al texto completo (gratis o de pago) [1177_1947601913479020](#) [pii]
- Enlace al texto completo (gratis o de pago) [1177/1947601913479020](#)

AUTORES / AUTHORS: - Ronald S; Awate S; Rath A; Carroll J; Galiano F; Dwyer D; Kleiner-Hancock H; Mathis JM; Vigod S; De Benedetti A

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology and the Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA, USA.

RESUMEN / SUMMARY: - The Toslod-like kinases (TLKs) are involved in chromatin assembly, DNA repair, and transcription. Two TLK genes exist in humans, and their expression is often dysregulated in cancer. TLKs phosphorylate Asf1 and Rad9, regulating double-strand break (DSB) repair and the DNA damage response (DDR). TLKs maintain genomic stability and are important therapeutic intervention targets. We identified specific inhibitors of TLKs from several compound libraries, some of which

belong to the family of phenothiazine antipsychotics. The inhibitors prevented the TLK-mediated phosphorylation of Rad9(S328) and impaired checkpoint recovery and DSB repair. The inhibitor thioridazine (THD) potentiated tumor killing with chemotherapy and also had activity alone. Staining for gamma-H2AX revealed few positive cells in untreated tumors, but large numbers in mice treated with low doxorubicin or THD alone, possibly the result of the accumulation of DSBs that are not promptly repaired as they may occur in the harsh tumor growth environment.

[963]

TÍTULO / TITLE: - Licochalcone a-induced human bladder cancer t24 cells apoptosis triggered by mitochondria dysfunction and endoplasmic reticulum stress.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:474272. doi: 10.1155/2013/474272. Epub 2013 Jul 7.

●● Enlace al texto completo (gratis o de pago) [1155/2013/474272](#)

AUTORES / AUTHORS: - Yuan X; Li D; Zhao H; Jiang J; Wang P; Ma X; Sun X; Zheng Q

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Xinjiang Endemic Phytomedicine Resources, Ministry of Education, School of Pharmacy, Shihezi University, Shihezi, Xinjiang 832002, China.

RESUMEN / SUMMARY: - Licochalcone A (LCA), a licorice chalconoid, is considered to be a bioactive agent with chemopreventive potential. This study investigated the mechanisms involved in LCA-induced apoptosis in human bladder cancer T24 cells. LCA significantly inhibited cells proliferation, increased reactive oxygen species (ROS) levels, and caused T24 cells apoptosis. Moreover, LCA induced mitochondrial dysfunction, caspase-3 activation, and poly-ADP-ribose polymerase (PARP) cleavage, which displayed features of mitochondria-dependent apoptotic signals. Besides, exposure of T24 cells to LCA triggered endoplasmic reticulum (ER) stress; as indicated by the enhancement in 78 kDa glucose-regulated protein (GRP 78), growth arrest and DNA damage-inducible gene 153/C/EBP homology protein (GADD153/CHOP) expression, ER stress-dependent apoptosis is caused by the activation of ER-specific caspase-12. All the findings from our study suggest that LCA initiates mitochondrial ROS generation and induces oxidative stress that consequently causes T24 cell apoptosis via the mitochondria-dependent and the ER stress-triggered signaling pathways.

[964]

TÍTULO / TITLE: - Ziyuglycoside II Inhibits the Growth of Human Breast Carcinoma MDA-MB-435 Cells via Cell Cycle Arrest and Induction of Apoptosis through the Mitochondria Dependent Pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Sep 3;14(9):18041-55. doi: 10.3390/ijms140918041.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140918041](https://doi.org/10.3390/ijms140918041)

AUTORES / AUTHORS: - Zhu X; Wang K; Zhang K; Huang B; Zhang J; Zhang Y; Zhu L; Zhou B; Zhou F

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Nuclear Medicine, Ministry of Health, Jiangsu Key Laboratory of Molecular Nuclear Medicine, Jiangsu Institute of Nuclear Medicine, Wuxi 214063, China. wangke@jsnm.org.

RESUMEN / SUMMARY: - Ziyuglycoside II is one of the major active compounds of *Sanguisorba officinalis* L., which has a wide range of clinical applications including hemostasis, antibiosis, anti-inflammation and anti-oxidation. This study investigated the effect of ziyuglycoside II on the growth of human breast carcinoma MDA-MB-435 cells for the first time. The results showed that ziyuglycoside II could significantly inhibit the growth of MDA-MB-435 cells through blocking cell cycle progression at G0/G1 and S phase as well as via inducing cell apoptosis. Accumulation of reactive oxygen species (ROS) was observed in the progression of cell cycle arrest, which was associated with the increased expression of cell cycle regulating factors, p53 and p21. Subsequent apoptosis induced by ziyuglycoside II was accompanied with the activation of mitochondrial pathway, in particular a decreased mitochondrial membrane potential (MMP) as well as increased Bax/Bcl-2 ratio, cytochrome c release and the activity of caspase-3 and caspase-9. In conclusion, our study was the first to report that ziyuglycoside II has inhibitory effect on the growth of MDA-MB-435 cells, which might become a potential therapeutic approach of breast cancer in the future.

[965]

TÍTULO / TITLE: - Emodin elicits cytotoxicity in human lung adenocarcinoma A549 cells through inducing apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Inflammopharmacology. 2013 Aug 22.

●● Enlace al texto completo (gratis o de pago) [1007/s10787-013-0186-4](https://doi.org/10.1007/s10787-013-0186-4)

AUTORES / AUTHORS: - Li WY; Ng YF; Zhang H; Guo ZD; Guo DJ; Kwan YW; Leung GP; Lee SM; Yu PH; Chan SW

INSTITUCIÓN / INSTITUTION: - Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China.

RESUMEN / SUMMARY: - This study investigated the mechanism of the cytotoxic effect of emodin, an active anthraquinone, on human lung adenocarcinoma A549 cells. In vitro growth inhibition and suppression on colony forming were used to evaluate the effects of emodin on A549 cells. Emodin's ability in changing the expressions of apoptosis-related genes was studied by real-time RT-PCR. Emodin could significantly inhibit the growth of A549 cells with IC50 = 16.85 mug/ml (~60 muM). It also concentration dependently inhibited the colony-forming ability of A549 cells with IC50 = 7.60 mug/ml

(~30 µM). Hallmarks of apoptosis, such as single-strand DNA breakage and DNA fragmentation, were observed in A549 cells treated with emodin. Emodin (72 h) treatment could up-regulate the gene expression of FASL ($p < 0.05$) and down-regulate the gene expression of C-MYC ($p < 0.01$), but induce no significant changes in the gene expressions of MCL1, GAPDH, BAX and CCND1. These results suggest that emodin could induce growth inhibition and apoptosis in A549 cells through modifying the extrinsic apoptotic pathways and the induction of cell cycle arrest.

[966]

TÍTULO / TITLE: - Matrine activates PTEN to induce growth inhibition and apoptosis in V600EBRAF harboring melanoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Jul 31;14(8):16040-57. doi: 10.3390/ijms140816040.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140816040](#)

AUTORES / AUTHORS: - Jin H; Sun Y; Wang S; Cheng X

INSTITUCIÓN / INSTITUTION: - School of Life Sciences and Technology, Tongji University, Shanghai 200092, China. joycejinhui@tongji.edu.cn

RESUMEN / SUMMARY: - Here, we report a natural chemical Matrine, which exhibits anti-melanoma potential with its PTEN activation mechanism. Matrine effectively inhibited proliferation of several carcinoma cell lines, including melanoma V600EBRAF harboring M21 cells. Flow cytometry analysis showed Matrine induced G0/G1 cell cycle arrest in M21 cells dose-dependently. Apoptosis in M21 cells induced by Matrine was identified by Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) analysis and Annexin-V/FITC staining. Molecular mechanistic study suggested that Matrine upregulated both mRNA level and protein expression level of phosphatase and tensin homolog deleted on chromosome ten (PTEN), leading to inhibition of the PI3K/Akt pathway. Downregulation of phosphor-Aktser473 by Matrine activated p21 and Bax, which contributed to G0/G1 cell cycle and apoptosis. Besides, Matrine enhanced the PI3K/Akt inhibition effects to inhibit the cell proliferation with PI3K inhibitor, LY2940002. In summary, our findings suggest Matrine is a promising antitumor drug candidate with its possible PTEN activation mechanisms for treating cancer diseases, such as melanomas.

[967]

TÍTULO / TITLE: - Cordycepin enhances cisplatin apoptotic effect through caspase/MAPK pathways in human head and neck tumor cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jul 25;6:983-98. doi: 10.2147/OTT.S45322. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S45322](#)

AUTORES / AUTHORS: - Chen YH; Wang JY; Pan BS; Mu YF; Lai MS; So EC; Wong TS; Huang BM

INSTITUCIÓN / INSTITUTION: - Department of Anesthesia, Chi-Mei Medical Center, Liouying, Tainan, Taiwan ; Department of Nursing, Min-Hwei College of Health Care Management, Tainan, Taiwan.

RESUMEN / SUMMARY: - **PURPOSE:** The present study aims to investigate whether the combination treatment of cordycepin (an extracted pure compound from *Cordyceps sinensis*) and cisplatin (a platinum-based chemotherapy drug) has better apoptotic effect in head and neck squamous cell carcinoma (HNSCC). **METHODS:** The apoptotic influences of cordycepin and/or cisplatin treatments to human OC3, OEC-M1, and FaDu HNSCC cells were investigated by morphological observations, viability assay, flow cytometry assay, and Western blotting methods. **RESULTS:** Data showed that the cell death phenomenon increased as the dosage of cordycepin or cisplatin increased, and it appeared more in cordycepin plus cisplatin cotreatment among three cell lines. Cell survival rates significantly decreased as the dosage of cordycepin or cisplatin increased, and the better apoptotic effects were observed in cotreatment. Cell cycle analysis further demonstrated that percentages of subG1 cells in cordycepin or cisplatin treatments significantly increased, suggesting that cells underwent apoptosis, and cordycepin plus cisplatin induced many more subG1 cells. Furthermore, cordycepin or cisplatin induced caspase-8, caspase-9, caspase-3, and poly adenosine diphosphate-ribose polymerase protein cleavages, and stimulated c-Jun NH2-terminal kinase, extracellular signal-regulated kinase, and p38 protein phosphorylations. Moreover, cordycepin plus cisplatin cotreatment significantly activated those proteins with much better effects among three cell lines. **CONCLUSION:** Cordycepin plus cisplatin have better apoptotic effect by activating caspase activation with possible MAPK pathway involvement in HNSCC cells.

[968]

TÍTULO / TITLE: - Mithramycin A induces apoptosis by regulating the mTOR/Mcl-1/tBid pathway in androgen-independent prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Clin Biochem Nutr. 2013 Sep;53(2):89-93. doi: 10.3164/jcbn.13-28. Epub 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [3164/jcbn.13-28](#)

AUTORES / AUTHORS: - Choi ES; Chung T; Kim JS; Lee H; Kwon KH; Cho NP; Cho SD

INSTITUCIÓN / INSTITUTION: - Department of Oral Pathology, School of Dentistry and Institute of Oral Bioscience, Brain Korea 21 Project, Chonbuk National University, Jeonju 561-756, Republic of Korea.

RESUMEN / SUMMARY: - Mithramycin A (Mith) is an aureolic acid-type polyketide produced by various soil bacteria of the genus *Streptomyces*. Mith inhibits myeloid cell leukemia-1 (Mcl-1) to induce apoptosis in prostate cancer, but the molecular

mechanism underlying this process has not been fully elucidated. The aim of this study was therefore to investigate the detailed molecular mechanism related to Mith-induced apoptosis in prostate cancer cells. Mith decreased the phosphorylation of mammalian target of rapamycin (mTOR) in both cell lines overexpressing phospho-mTOR compared to RWPE-1 human normal prostate epithelial cells. Mith significantly induced truncated Bid (tBid) and siRNA-mediated knock-down of Mcl-1 increased tBid protein levels. Moreover, Mith also inhibited the phosphorylation of mTOR on serine 2448 and Mcl-1, and increased tBid protein in prostate tumors in athymic nude mice bearing DU145 cells as xenografts. Thus, Mith acts as an effective tumor growth inhibitor in prostate cancer cells through the mTOR/Mcl-1/tBid signaling pathway.

[969]

TÍTULO / TITLE: - Evidence for two modes of synergistic induction of apoptosis by mapatumumab and oxaliplatin in combination with hyperthermia in human colon cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 27;8(8):e73654. doi: 10.1371/journal.pone.0073654.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073654](#)

AUTORES / AUTHORS: - Song X; Kim SY; Lee YJ

INSTITUCIÓN / INSTITUTION: - Department of Surgery, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America.

RESUMEN / SUMMARY: - Colorectal cancer is the third leading cause of cancer-related mortality in the world—the main cause of death from colorectal cancer is hepatic metastases, which can be treated with isolated hepatic perfusion (IHP). Searching for the most clinically relevant approaches for treating colorectal metastatic disease by isolated hepatic perfusion (IHP), we developed the application of oxaliplatin concomitantly with hyperthermia and humanized death receptor 4 (DR4) antibody mapatumumab (Mapa), and investigated the molecular mechanisms of this multimodality treatment in human colon cancer cell lines CX-1 and HCT116 as well as human colon cancer stem cells Tu-12, Tu-21 and Tu-22. We showed here, in this study, that the synergistic effect of the multimodality treatment-induced apoptosis was caspase dependent and activated death signaling via both the extrinsic apoptotic pathway and the intrinsic pathway. Death signaling was activated by c-Jun N-terminal kinase (JNK) signaling which led to Bcl-xL phosphorylation at serine 62, decreasing the anti-apoptotic activity of Bcl-xL, which contributed to the intrinsic pathway. The downregulation of cellular FLICE inhibitory protein long isoform (c-FLIPL) in the extrinsic pathway was accomplished through ubiquitination at lysine residue (K) 195 and protein synthesis inhibition. Overexpression of c-FLIPL mutant (K195R) and Bcl-xL mutant (S62A) completely abrogated the synergistic effect. The successful outcome of this study supports the application of multimodality strategy to patients with

colorectal hepatic metastases who fail to respond to standard chemoradiotherapy that predominantly targets the mitochondrial apoptotic pathway.

[970]

TÍTULO / TITLE: - Cucurmosin induces the apoptosis of human pancreatic cancer CFPAC-1 cells by inactivating the PDGFR-beta signalling pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacol Rep. 2013;65(3):682-8.

AUTORES / AUTHORS: - Xie J; Wang C; Zhang B; Yang A; Yin Q; Huang H; Chen M

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Fujian Medical University, Fuzhou 350004, Fujian, China. xiejm1@sina.com or hhuang2@aliyun.com.

RESUMEN / SUMMARY: - Background: Pancreatic cancer treatment is limited and effective drugs are needed. We investigated cucurmosin (CUS)-induced apoptosis in cystic fibrosis pancreatic adenocarcinoma cells (CFPAC-1) and a possible mechanism of action to evaluate the clinical application potential of this new Type I ribosome-inactivating protein. Methods: We analyzed the growth inhibition and apoptosis of CFPAC-1 cells via methylthiazol tetrazolium assay and fluorescence-activated cell sorting. Western blot was used to analyze the protein levels of caspase 3, bcl-2, caspase 9, platelet-derived growth factor receptor (PDGFR)-beta, PI3K, Akt, p-Akt, the mammalian target of rapamycin (mTOR), p-mTOR, P70S6K-alpha, p-P70S6K-alpha, 4E-BP1, p-4E-BP1 and p-Bad after CUS intervention. The mRNA expression of PDGFR-beta was analyzed using reverse transcription polymerase chain reaction. Results: CUS inhibited the proliferation of pancreatic cancer cells. The induction of apoptosis depended on the CUS dose and incubation time. The drug inhibited all of the examined proteins in the PI3K/Akt/mTOR signalling pathway and induced the active fragments of caspase 3 and caspase 9. CUS downregulated PDGFR-beta expression but no significant change was observed at the mRNA level. Conclusion: CUS strongly inhibits the growth of CFPAC-1 by inducing cell apoptosis. CUS downregulated the expression of PDGFR-beta at the protein level and induced the apoptosis of CFPAC-1 through the PI3K/Akt/mTOR signalling pathway.

[971]

TÍTULO / TITLE: - Apoptotic and Autophagic Effects of Sesbania grandiflora Flowers in Human Leukemic Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e71672. doi: 10.1371/journal.pone.0071672.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0071672](#)

AUTORES / AUTHORS: - Roy R; Kumar D; Chakraborty B; Chowdhury C; Das P

INSTITUCIÓN / INSTITUTION: - Cancer Biology and Inflammatory Disorder Division, CSIR-Indian Institute of Chemical Biology, Kolkata, West Bengal, India.

RESUMEN / SUMMARY: - BACKGROUND: Identification of cytotoxic compounds that induce apoptosis has been the mainstay of anti-cancer therapeutics for several decades. In recent years, focus has shifted to inducing multiple modes of cell death coupled with reduced systemic toxicity. The plant *Sesbania grandiflora* is widely used in Indian traditional medicine for the treatment of a broad spectrum of diseases. This encouraged us to investigate into the anti-proliferative effect of a fraction (F2) isolated from *S. grandiflora* flowers in cancer cells and delineate the underlying involvement of apoptotic and autophagic pathways. PRINCIPAL FINDINGS: Using MTT based cell viability assay, we evaluated the cytotoxic potential of fraction F2. It was the most effective on U937 cells (IC₅₀ 18.6 microg/ml). Inhibition of growth involved enhancement of Annexin V positivity. This was associated with elevated reactive oxygen species generation, measured by flow cytometry and reduced oxygen consumption - both effects being abrogated by anti-oxidant NAC. This caused stimulation of pro-apoptotic proteins and concomitant inhibition of anti-apoptotic protein expressions inducing mitochondrial depolarization, as measured by flow cytometry and release of cytochrome c. Interestingly, even with these molecular features of apoptosis, F2 was able to alter Atg protein levels and induce LC3 processing. This was accompanied by formation of autophagic vacuoles as revealed by fluorescence and transmission electron microscopy - confirming the occurrence of autophagy. Eventually, F2 triggered caspase cascade - executioners of programmed cell death and AIF translocation to nuclei. This culminated in cleavage of the DNA repair enzyme, poly (ADP-ribose) polymerase that caused DNA damage as proved by staining with Hoechst 33258 leading to cell death. CONCLUSIONS: The findings suggest fraction F2 triggers pro-oxidant activity and mediates its cytotoxicity in leukemic cells via apoptosis and autophagy. Thus, it merits consideration and further investigation as a therapeutic option for the treatment of leukemia.

[972]

TÍTULO / TITLE: - Copper oxide nanoparticles induced mitochondria mediated apoptosis in human hepatocarcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e69534. doi: 10.1371/journal.pone.0069534. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069534](https://doi.org/10.1371/journal.pone.0069534)

AUTORES / AUTHORS: - Siddiqui MA; Alhadlaq HA; Ahmad J; Al-Khedhairi AA; Musarrat J; Ahamed M

INSTITUCIÓN / INSTITUTION: - Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia.

RESUMEN / SUMMARY: - Copper oxide nanoparticles (CuO NPs) are heavily utilized in semiconductor devices, gas sensor, batteries, solar energy converter, microelectronics and heat transfer fluids. It has been reported that liver is one of the target organs for

nanoparticles after they gain entry into the body through any of the possible routes. Recent studies have shown cytotoxic response of CuO NPs in liver cells. However, the underlying mechanism of apoptosis in liver cells due to CuO NPs exposure is largely lacking. We explored the possible mechanisms of apoptosis induced by CuO NPs in human hepatocellular carcinoma HepG2 cells. Prepared CuO NPs were spherical in shape with a smooth surface and had an average diameter of 22 nm. CuO NPs (concentration range 2-50 microg/ml) were found to induce cytotoxicity in HepG2 cells in dose-dependent manner, which was likely to be mediated through reactive oxygen species generation and oxidative stress. Tumor suppressor gene p53 and apoptotic gene caspase-3 were up-regulated due to CuO NPs exposure. Decrease in mitochondrial membrane potential with a concomitant increase in the gene expression of bax/bcl2 ratio suggested that mitochondria mediated pathway involved in CuO NPs induced apoptosis. This study has provided valuable insights into the possible mechanism of apoptosis caused by CuO NPs at in vitro level. Underlying mechanism(s) of apoptosis due to CuO NPs exposure should be further investigated at in vivo level.

[973]

TÍTULO / TITLE: - Calcearia carbonica induces apoptosis in cancer cells in p53-dependent manner via an immuno-modulatory circuit.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Sep 21;13(1):230.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1472-6882-13-230](#)

AUTORES / AUTHORS: - Saha S; Hossain DM; Mukherjee S; Mohanty S; Mazumdar M; Mukherjee S; Ghosh UK; Nayek C; Raveendar C; Khurana A; Chakrabarty R; Sa G; Das T

RESUMEN / SUMMARY: - BACKGROUND: Complementary medicines, including homeopathy, are used by many patients with cancer, usually alongside with conventional treatment. However, the molecular mechanisms underneath the anticancer effect, if any, of these medicines have still remained unexplored. To this end we attempted to evaluate the efficacy of calcarea carbonica, a homeopathic medicine, as an anti-cancer agent and to delineate the detail molecular mechanism(s) underlying calcarea carbonica-induced tumor regression. RESULTS: Interestingly, although calcarea carbonica administration to Ehrlich's ascites carcinoma (EAC)- and Sarcoma-180 (S-180)-bearing Swiss albino mice resulted in 30-35% tumor cell apoptosis, it failed to induce any significant cell death in ex vivo conditions. These results prompted us to examine whether calcarea carbonica employs the immuno-modulatory circuit in asserting its anti-tumor effects. In tumor-bearing mice, there was profound depletion of CD4+ and CD8+ cells in peripheral blood, dominance of type-2 T helper cells and inhibition of T cell proliferation. Calcarea carbonica in turn prevented such loss of effector T cell repertoire, reversed type-2 cytokine bias and attenuated tumor-induced inhibition of T cell proliferation in tumor-bearing host. To confirm the role of immune system in calcarea carbonica-induced cancer cell death, a battery of

cancer cells were co-cultured with calcarea carbonica-primed T cells. Our results indicated a “two-step” mechanism of the induction of apoptosis in tumor cells by calcarea carbonica i.e., (1) activation of the immune system of the host; and (2) induction of cancer cell apoptosis via immunomodulatory circuit in p53-dependent manner by down-regulating Bcl-2:Bax ratio. Bax up-regulation resulted in mitochondrial transmembrane potential loss and cytochrome c release followed by activation of caspase cascade. Knocking out of p53 by RNA-interference inhibited calcarea carbonica-induced apoptosis thereby confirming the contribution of p53. CONCLUSION: These observations delineate the significance of immuno-modulatory circuit during calcarea carbonica-mediated tumor apoptosis. The molecular mechanism identified may serve as a platform for involving calcarea carbonica into immunotherapeutic strategies for effective tumor regression.

[974]

TÍTULO / TITLE: - 2-methoxyestradiol induces mitotic arrest, apoptosis, and synergistic cytotoxicity with arsenic trioxide in human urothelial carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e68703. doi: 10.1371/journal.pone.0068703.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0068703](#)

AUTORES / AUTHORS: - Kuo KL; Lin WC; Ho IL; Chang HC; Lee PY; Chung YT; Hsieh JT; Pu YS; Shi CS; Huang KH

INSTITUCIÓN / INSTITUTION: - Department of Urology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan.

RESUMEN / SUMMARY: - 2-Methoxyestradiol (2-ME), an endogenous derivative of 17beta-estradiol, has been reported to elicit antiproliferative responses in various tumors. In this study, we investigated the effects of 2-ME on cell viability, proliferation, cell cycle, and apoptosis in human urothelial carcinoma (UC) cell lines. We used two high-grade human bladder UC cell lines (NTUB1 and T24). After treatment with 2-ME, the cell viability and apoptosis were measured by MTT assay and flow cytometry (fluorescence-activated cell sorting), with annexin V-FITC staining and propidium iodide (PI) labeling. DNA fragmentation was analyzed by agarose gel electrophoresis. Flow cytometry with PI labeling was used for the cell cycle analyses. The protein levels of caspase activations, poly (ADP-ribose) polymerase (PARP) cleavage, phospho-histone H2A.X, phospho-Bad, and cell cycle regulatory molecules were measured by Western blot. The effects of the drug combinations were analyzed using the computer software, CalcuSyn. We demonstrated that 2-ME effectively induces dose-dependent cytotoxicity and apoptosis in human UC cells after 24 h exposure. DNA fragmentation, PARP cleavage, and caspase-3, 7, 8, 9 activations can be observed with 2-ME-induced apoptosis. The decreased phospho-Bad (Ser136 and Ser155) and mitotic arrest of the cell cycle in the process of apoptosis after 2-ME treatment was remarkable. In response to mitotic arrest, the mitotic forms of cdc25C,

phospho-cdc2, cyclin B1, and phospho-histone H3 (Ser10) were activated. In combination with arsenic trioxide (As₂O₃), 2-ME elicited synergistic cytotoxicity (combination index <1) in UC cells. We concluded that 2-ME significantly induces apoptosis through decreased phospho-Bad and arrests bladder UC cells at the mitotic phase. The synergistic antitumor effect with As₂O₃ provides a novel implication in clinical treatment of UC.

[975]

TÍTULO / TITLE: - OCT4 promotes tumorigenesis and inhibits apoptosis of cervical cancer cells by miR-125b/BAK1 pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 8;4:e760. doi: 10.1038/cddis.2013.272.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cddis.2013.272](#)

AUTORES / AUTHORS: - Wang YD; Cai N; Wu XL; Cao HZ; Xie LL; Zheng PS

INSTITUCIÓN / INSTITUTION: - Department of Reproductive Medicine, First Affiliated Hospital, Xi'an Jiaotong University of Medical School, Xi'an, People's Republic of China.

RESUMEN / SUMMARY: - Octamer-binding transcription factor 4 (OCT4) is a key regulatory gene that maintains the pluripotency and self-renewal properties of embryonic stem cells. Although there is emerging evidence that it can function as oncogene in several cancers, the role in mediating cervical cancer remains unexplored. Here we found that OCT4 protein expression showed a pattern of gradual increase from normal cervix to cervical carcinoma in situ and then to invasive cervical cancer. Overexpression of OCT4 in two types of cervical cancer cells promotes the carcinogenesis, and inhibits cancer cell apoptosis. OCT4 induces upregulation of miR-125b through directly binding to the promoter of miR-125b-1 confirmed by chromatin immunoprecipitation analysis. MiRNA-125b overexpression suppressed apoptosis and expression of BAK1 protein. In contrast, miR-125b sponge impaired the anti-apoptotic effect of OCT4, along with the upregulated expression of BAK1. Significantly, Luciferase assay showed that the activity of the wild-type BAK1 3'-untranslated region reporter was suppressed and this suppression was diminished when the miR-125b response element was mutated or deleted. In addition, we observed negative correlation between levels of BAK1 and OCT4, and positive between OCT4 and miR-125b in primary cervical cancers. These findings suggest an undescribed regulatory pathway in cervical cancer, by which OCT4 directly induces expression of miR-125b, which inhibits its direct target BAK1, leading to suppression of cervical cancer cell apoptosis.

[976]

TÍTULO / TITLE: - Glucocalyxin A, a negative Akt regulator, specifically induces apoptosis in human brain glioblastoma U87MG cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Biochim Biophys Sin (Shanghai). 2013 Sep 15.

●● Enlace al texto completo (gratis o de pago) [1093/abbs/gmt097](https://doi.org/10.1093/abbs/gmt097)

AUTORES / AUTHORS: - Xiao X; Cao W; Jiang X; Zhang W; Zhang Y; Liu B; Cheng J; Huang H; Huo J; Zhang X

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Xijing Institute of Clinical Neuroscience, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China.

RESUMEN / SUMMARY: - Akt is becoming an attractive target in the development of anti-tumor agents. In the present study, we aimed to discover novel negative Akt regulators against malignant glioma. An Akt regulator screening platform performed in an Akt-GFP overexpression cell line was developed, and natural product library was screened and evaluated using this platform. In addition, the cytotoxic effect of the regulator was detected by MTT assay. Cell apoptosis was assayed by Hoechst 33342 staining and flow cytometry analysis. Afterwards, the apoptotic signaling pathway was investigated by western blot analysis. Glaucoalyxin A, isolated from *Rabdosia japonica*, was identified as a potent negative regulator of Akt. In human-derived malignant glioma U87MG cells, glaucoalyxin A inhibited Akt phosphorylation, suppressed proliferation, and promoted apoptosis in a dose-dependent manner, but not in normal glial cells. Furthermore, glaucoalyxin A activated caspase-3, decreased BAD phosphorylation, and reduced the expression of X-linked inhibitor of apoptosis protein. Taken together, these results indicated that glaucoalyxin A may become a promising candidate in the treatment of malignant glioma.

[977]

TÍTULO / TITLE: - Reactive oxygen species mediate isoalantolactone-induced apoptosis in human prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Molecules*. 2013 Aug 5;18(8):9382-96. doi: 10.3390/molecules18089382.

●● Enlace al texto completo (gratis o de pago) [3390/molecules18089382](https://doi.org/10.3390/molecules18089382)

AUTORES / AUTHORS: - Rasul A; Di J; Millimouno FM; Malhi M; Tsuji I; Ali M; Li J; Li X

INSTITUCIÓN / INSTITUTION: - The Key Laboratory of Molecular Epigenetics of MOE, Institute of Genetics and Cytology, Northeast Normal University, Changchun 130024, China.

RESUMEN / SUMMARY: - Isoalantolactone, a medicinal plant-derived natural compound, is known to induce apoptosis in various cancer cell lines. However, its effect on apoptosis in prostate cancer cells has not been addressed. Thus, we examined the effects of isoalantolactone on prostate cancer cells. It was found that isoalantolactone inhibits growth of both androgen-sensitive (LNCaP) as well as androgen-independent (PC3 and DU-145) prostate cancer cells in a dose-dependent manner. Furthermore, our results indicate that isoalantolactone-induced apoptosis in prostate cancer PC3 cells is associated with the generation of ROS and dissipation of mitochondrial membrane potential (Deltapsim). In addition, isoalantolactone triggers apoptosis in prostate

cancer cells via up-regulation of Bax, down-regulation of Bcl-2, survivin, and significant activation of caspase-3. Isoalantolactone-induced apoptosis is markedly abrogated when the cells were pretreated with N-acetylcysteine (NAC), a specific ROS inhibitor, suggesting that the apoptosis-inducing effect of isoalantolactone in prostate cancer cells is mediated by reactive oxygen species. These findings indicate that isoalantolactone induces reactive oxygen species-dependent apoptosis in prostate cancer cells via a novel mechanism involving inhibition of survivin and provide the rationale for further in vivo and preclinical investigation of isoalantolactone against human prostate cancer.

[978]

TÍTULO / TITLE: - Plumbagin induces the apoptosis of human tongue carcinoma cells through the mitochondria-mediated pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Med Sci Monit Basic Res. 2013 Aug 28;19:228-36. doi: 10.12659/MSMBR.884004.

●● Enlace al texto completo (gratis o de pago) [12659/MSMBR.884004](#)

AUTORES / AUTHORS: - Qiu JX; He YQ; Wang Y; Xu RL; Qin Y; Shen X; Zhou SF; Mao ZF

INSTITUCIÓN / INSTITUTION: - Department of Stomatology, Fourth Affiliated Hospital of Nanchang University, Nanchang, P.R. China and School of Public Health, Wuhan University, Wuhan, P.R. China.

RESUMEN / SUMMARY: - Background Plumbagin, a quinonoid constituent isolated from the root of *Plumbago zeylanica* L., has been proven to possess anti-tumor activity both in vitro and in vivo. However, its anti-tumor properties for human tongue carcinoma have not been reported. This study aimed to investigate the inhibitory effect and the underlying mechanism of plumbagin on the growth of human tongue carcinoma cells. Material and Methods Cell proliferation ability was detected by EdU incorporation assay and colony formation assay. Cell-cycle distribution was determined by flow cytometric analysis using propidium iodide (PI) staining. Cellular apoptosis was then evaluated by flow cytometry and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Western blotting was applied to assay the expression of Bax and Bcl-2. Results Plumbagin inhibited the growth and proliferation of Tca8113 cells in vitro in a concentration- and time-dependent manner. The cell cycles of plumbagin-treated Tca8113 cells were arrested at the G2/M phase. Cells treated with plumbagin presented the characteristic morphological changes of apoptosis. The ratio of Bax/Bcl-2 was raised by plumbagin in a concentration-dependent manner. Conclusions These results indicate that plumbagin induces the apoptosis of Tca8113 cells through mitochondria-mediated pathway.

[979]

TÍTULO / TITLE: - 2'-Hydroxy C16-Ceramide Induces Apoptosis-Associated Proteomic Changes in C6 Glioma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Proteome Res. 2013 Oct 4;12(10):4366-4375. Epub 2013 Sep 12.

●● Enlace al texto completo (gratis o de pago) [1021/pr4003432](#)

AUTORES / AUTHORS: - Kota V; Dhople VM; Fullbright G; Smythe NM; Szulc ZM; Bielawska A; Hama H

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston, South Carolina 29425, United States.

RESUMEN / SUMMARY: - Ceramide is a bioactive sphingolipid involved in regulation of numerous cell signaling pathways. Evidence is accumulating that differences in ceramide structure, such as N-acyl chain length and desaturation of sphingoid base, determine the biological activities of ceramide. Using synthetic [®]-2'-hydroxy-C16-ceramide, which is the naturally occurring stereoisomer, we demonstrate that this ceramide has more potent pro-apoptotic activity compared to its (S) isomer or non-hydroxylated C16-ceramide. Upon exposure to [®]-2'-hydroxy-ceramide, C6 glioma cells rapidly underwent apoptosis as indicated by caspase-3 activation, PARP cleavage, chromatin condensation, and annexin V stain. A 2D gel proteomics analysis identified 28 proteins whose levels were altered during the initial 3 h of exposure. Using the list of 28 proteins, we performed a software-assisted pathway analysis to identify possible signaling events that would result in the observed changes. The result indicated that Akt and MAP kinase pathways are among the possible pathways regulated by [®]-2'-hydroxy-ceramide. Experimental validation confirmed that 2'-hydroxy-ceramide significantly altered phosphorylation status of Akt and its downstream effector GSK3beta, as well as p38, ERK1/2, and JNK1/2 MAP kinases. Unexpectedly, robust phosphorylation of Akt was observed within 1 h of exposure to 2'-hydroxy-ceramide, followed by dephosphorylation. Phosphorylation status of MAPKs showed a complex pattern, in which rapid phosphorylation of ERK1/2 was followed by dephosphorylation of p38 and ERK1/2 and phosphorylation of the 46 kDa isoform of JNK1/2. These data indicate that [®]-2'-hydroxy-ceramide regulates multiple signaling pathways by affecting protein kinases and phosphatases with kinetics distinct from that of the extensively studied non-hydroxy-ceramide or its unnatural stereoisomer.

[980]

TÍTULO / TITLE: - CBP Activity Mediates Effects of the Histone Deacetylase Inhibitor Butyrate on WNT Activity and Apoptosis in Colon Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cancer. 2013 Jul 15;4(6):481-90. doi: 10.7150/jca.6583. Print 2013.

●● Enlace al texto completo (gratis o de pago) [7150/jca.6583](#)

AUTORES / AUTHORS: - Lazarova DL; Chiaro C; Wong T; Drago E; Rainey A; O'Malley S; Bordonaro M

INSTITUCIÓN / INSTITUTION: - 1. Department of Basic Sciences, The Commonwealth Medical College, 525 Pine Street, Scranton, PA 18509, USA.

RESUMEN / SUMMARY: - Mutations in the WNT/beta-catenin pathway are responsible for initiating the majority of colorectal cancers (CRCs). We have previously shown that hyperactivation of this signaling by histone deacetylase inhibitors (HDACis) such as butyrate, a fermentation product of dietary fiber, promotes CRC cell apoptosis. The extent of association between beta-catenin and the transcriptional coactivator CREB-binding protein (CBP) influences WNT/catenin signaling and, therefore, colonic cell physiology. CBP functions as a histone acetylase (HAT); therefore, we hypothesized that the modulation of WNT/catenin activity by CBP modifies the ability of the HDACi butyrate to hyperinduce WNT signaling and apoptosis in CRC cells. Our findings indicate that CBP affects the hyperinduction of WNT activity by butyrate. ICG-001, which specifically blocks association between CBP and beta-catenin, abrogates the butyrate-triggered increase in the number of CRC cells with high levels of WNT/catenin signaling. Combination treatment of CRC cells with ICG-001 and butyrate results in cell type-specific effects on apoptosis. Further, both butyrate and ICG-001 repress CRC cell proliferation, with additive effects in suppressing cell growth. Our study strongly suggests that ICG-001-like agents would be effective against butyrate/HDACi-resistant CRC cells. Therefore, ICG-001-like agents may represent an important therapeutic option for CRCs that exhibit low-fold hyperactivation of WNT activity and apoptosis in the presence of HDACis. The findings generated from this study may lead to approaches that utilize modulation of CBP activity to facilitate CRC therapeutic or chemopreventive strategies.

[981]

TÍTULO / TITLE: - Bile acids induce apoptosis selectively in androgen-dependent and -independent prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PeerJ. 2013 Aug 8;1:e122. doi: 10.7717/peerj.122. Print 2013.

●● Enlace al texto completo (gratis o de pago) [7717/peerj.122](#)

AUTORES / AUTHORS: - Goldberg AA; Titorenko VI; Beach A; Sanderson JT

INSTITUCIÓN / INSTITUTION: - INRS-Institut Armand-Frappier, Laval, QC, Canada.

RESUMEN / SUMMARY: - Prostate cancer is a prevalent age-related disease in North America, accounting for about 15% of all diagnosed cancers. We have previously identified lithocholic acid (LCA) as a potential chemotherapeutic compound that selectively kills neuroblastoma cells while sparing normal human neurons. Now, we report that LCA inhibits the proliferation of androgen-dependent (AD) LNCaP prostate cancer cells and that LCA is the most potent bile acid with respect to inducing apoptosis in LNCaP as well as androgen-independent (AI) PC-3 cells, without killing

RWPE-1 immortalized normal prostate epithelial cells. In LNCaP and PC-3 cells, LCA triggered the extrinsic pathway of apoptosis and cell death induced by LCA was partially dependent on the activation of caspase-8 and -3. Moreover, LCA increased cleavage of Bid and Bax, down-regulation of Bcl-2, permeabilization of the mitochondrial outer membrane and activation of caspase-9. The cytotoxic actions of LCA occurred despite the inability of this bile acid to enter the prostate cancer cells with about 98% of the nominal test concentrations present in the extracellular culture medium. With our findings, we provide evidence to support a mechanism of action underlying the broad anticancer activity of LCA in various human tissues.

[982]

TÍTULO / TITLE: - Inhibition of PPARalpha Induces Cell Cycle Arrest and Apoptosis, and Synergizes with Glycolysis Inhibition in Kidney Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e71115. doi: 10.1371/journal.pone.0071115.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0071115](#)

AUTORES / AUTHORS: - Abu Aboud O; Wettersten HI; Weiss RH

INSTITUCIÓN / INSTITUTION: - Division of Nephrology, Department of Internal Medicine, University of California Davis, Davis, California, United States of America ; Comparative Pathology Graduate Group, University of California Davis, Davis, California, United States of America.

RESUMEN / SUMMARY: - Renal cell carcinoma (RCC) is the sixth most common cancer in the US. While RCC is highly metastatic, there are few therapeutic options available for patients with metastatic RCC, and progression-free survival of patients even with the newest targeted therapeutics is only up to two years. Thus, novel therapeutic targets for this disease are desperately needed. Based on our previous metabolomics studies showing alteration of peroxisome proliferator-activated receptor alpha (PPARalpha) related events in both RCC patient and xenograft mice materials, this pathway was further examined in the current study in the setting of RCC. PPARalpha is a nuclear receptor protein that functions as a transcription factor for genes including those encoding enzymes involved in energy metabolism; while PPARalpha has been reported to regulate tumor growth in several cancers, it has not been evaluated in RCC. A specific PPARalpha antagonist, GW6471, induced both apoptosis and cell cycle arrest at G0/G1 in VHL(+) and VHL(-) RCC cell lines (786-O and Caki-1) associated with attenuation of the cell cycle regulatory proteins c-Myc, Cyclin D1, and CDK4; this data was confirmed as specific to PPARalpha antagonism by siRNA methods. Interestingly, when glycolysis was blocked by several methods, the cytotoxicity of GW6471 was synergistically increased, suggesting a switch to fatty acid oxidation from glycolysis and providing an entirely novel therapeutic approach for RCC.

[983]

TÍTULO / TITLE: - Atmospheric Pressure Room Temperature Plasma Jets Facilitate Oxidative and Nitrate Stress and Lead to Endoplasmic Reticulum Stress Dependent Apoptosis in HepG2 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 27;8(8):e73665. doi: 10.1371/journal.pone.0073665.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073665](https://doi.org/10.1371/journal.pone.0073665)

AUTORES / AUTHORS: - Zhao S; Xiong Z; Mao X; Meng D; Lei Q; Li Y; Deng P; Chen M; Tu M; Lu X; Yang G; He G

INSTITUCIÓN / INSTITUTION: - The Genetic Engineering International Cooperation Base of Chinese Ministry of Science and Technology, The Key Laboratory of Molecular Biophysics of Chinese Ministry of Education, College of Life Science and Technology, Huazhong University of Science & Technology (HUST), Wuhan, China.

RESUMEN / SUMMARY: - Atmospheric pressure room temperature plasma jets (APRTP-Js) that can emit a mixture of different active species have recently found entry in various medical applications. Apoptosis is a key event in APRTP-Js-induced cellular toxicity, but the exact biological mechanisms underlying remain elusive. Here, we explored the role of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in APRTP-Js-induced apoptosis using in vitro model of HepG2 cells. We found that APRTP-Js facilitated the accumulation of ROS and RNS in cells, which resulted in the compromised cellular antioxidant defense system, as evidenced by the inactivation of cellular antioxidants including glutathione (GSH), superoxide dismutase (SOD) and catalase. Nitrotyrosine and protein carbonyl content analysis indicated that APRTP-Js treatment caused nitrate and oxidative injury of cells. Meanwhile, intracellular calcium homeostasis was disturbed along with the alteration in the expressions of GRP78, CHOP and pro-caspase12. These effects accumulated and eventually culminated into the cellular dysfunction and endoplasmic reticulum stress (ER stress)-mediated apoptosis. The apoptosis could be markedly attenuated by N-acetylcysteine (NAC, a free radical scavenger), which confirmed the involvement of oxidative and nitrate stress in the process leading to HepG2 cell apoptosis by APRTP-Js treatment.

[984]

TÍTULO / TITLE: - Differential effects of thapsigargin analogues on apoptosis of prostate cancer cells: Complex regulation by intracellular calcium.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - FEBS J. 2013 Aug 8. doi: 10.1111/febs.12475.

●● Enlace al texto completo (gratis o de pago) [1111/febs.12475](https://doi.org/10.1111/febs.12475)

AUTORES / AUTHORS: - Dubois C; Vanden Abeele F; Sehgal P; Olesen C; Junker S; Christensen SB; Prevarskaya N; Moller JV

INSTITUCIÓN / INSTITUTION: - Inserm U1003, Equipe labellisée par la Ligue Nationale Contre le Cancer, Université des Sciences et Technologies de Lille (USTL), Villeneuve

d'Ascq, France; Center for Membrane Pumps in Cells and Diseases, Danish Research Foundation, Aarhus, Denmark.

RESUMEN / SUMMARY: - The inhibition of sarcoplasmic reticulum Ca²⁺-ATPase (SERCA) by thapsigargin (Tg) and Tg-type analogues is considered to trigger cell death by activation of apoptotic pathways. Some of these analogues may be useful as antineoplastic agents after appropriate targeting as peptide conjugated prodrugs to cancer cells. With this in mind, this study evaluates the effect on LNCaP androgen-sensitive cancer cells of thapsigargin substituted with 12-aminododecanoyl linkers and Leu (Leu-8ADT), aspartate (Asp-8ADT) or Boc-8ADT. Our results show that both Leu-8ADT and Asp-8ADT result in rapid ER calcium depletion and an influx of calcium across the plasma membrane by activation of store-operated calcium entry. By contrast, ER Ca²⁺ depletion by Boc-8ADT is a very slow process that does not perceptibly increase cytosolic Ca²⁺ and activate store-operated calcium entry, because the inhibition of SERCA with this compound is very slow. Nevertheless, we find that Boc-8ADT is a more efficient inducer of apoptosis than both Tg and Leu-8ADT. Compared with Tg and the other analogues, apoptosis induced by Asp-8ADT is very modest, although this compound also activates store-operated calcium entry and at high concentrations (1 μm) causes severe morphological changes, reflecting decreased cell viability. We conclude that many factors need to be considered for optimization of these compounds in antineoplastic drug design. Among these ER stress induced by Ca²⁺ endoplasmic reticulum mobilization seems particularly important, whereas the early cytosolic increase of Ca²⁺ concentration preceding the executive phase of apoptosis appears to be of no, or little, consequence for a subsequent apoptotic effect.

[985]

TÍTULO / TITLE: - T-type calcium channel blockers inhibit autophagy and promote apoptosis of malignant melanoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pigment Cell Melanoma Res. 2013 Aug 12. doi: 10.1111/pcmr.12155.

●● Enlace al texto completo (gratis o de pago) [1111/pcmr.12155](#)

AUTORES / AUTHORS: - Das A; Pushparaj C; Herreros J; Nager M; Vilella R; Portero M; Pamplona R; Matias-Guiu X; Marti RM; Canti C

INSTITUCIÓN / INSTITUTION: - UdL-IRBLleida, Lleida, España.

RESUMEN / SUMMARY: - We have recently reported that human melanoma cells express a variety of voltage-gated calcium (Ca²⁺) channel types, including low-voltage-activated T-type channels that play a significant role in melanoma cell cycle progression. Here, we challenged melanoma metastatic cells with T-type channel blockers of clinical use and found a dual effect on cell viability: (i) a reduction in the proliferation rate, through a halt in the progression to the G1-S phase; and (ii) a promotion of cell death that was partially dependent on the activation of caspases. An

in-depth analysis of the death process showed that the apoptotic pathway is preceded by endoplasmic reticulum stress and the subsequent inhibition of the basal macroautophagy which is active in these cells. The effects of pharmacological blockers on Ca²⁺ homeostasis, autophagy, and cell death were mimicked by T-type channel gene silencing. These results provide the basis for a new pharmacological and/or gene silencing approach toward tackling melanoma metastasis.

[986]

TÍTULO / TITLE: - AMP-Activated Protein Kinase alpha 2 Isoform Suppression in Primary Breast Cancer Alters AMPK Growth Control and Apoptotic Signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genes Cancer. 2013 Jan;4(1-2):3-14. doi: 10.1177/1947601913486346.

- Enlace al texto completo (gratis o de pago) [1177_1947601913486346](#) [pii]
- Enlace al texto completo (gratis o de pago) [1177/1947601913486346](#)

AUTORES / AUTHORS: - Fox MM; Phoenix KN; Kopsiaftis SG; Claffey KP

INSTITUCIÓN / INSTITUTION: - Center for Vascular Biology, University of Connecticut Health Center, Farmington, CT, USA ; Department of Cell Biology, University of Connecticut Health Center, Farmington, CT, USA.

RESUMEN / SUMMARY: - Adenosine monophosphate-activated protein kinase (AMPK) is a metabolic regulator that promotes energy conservation and restoration when cells are exposed to nutrient stress. Given the high metabolic requirement of cancer cells, AMPK activation has been suggested as a potential preventative and therapeutic target. However, previous findings have shown that AMPK activity is diminished in some cancers. Expression of the 2 catalytic isoforms, AMPKalpha1 and AMPKalpha2, was evaluated in primary breast cancer and matched nontumor-adjacent tissue samples using immunohistochemistry. AMPK-dependent growth signaling events were examined in primary human mammary epithelial cells (HMECs) using RNAi to understand the importance of AMPKalpha2 in normal growth regulation. To test whether AMPKalpha2 would reinstate growth control and apoptotic mechanisms in breast cancer cells, metabolic stress assays and tumor xenografts were performed in MCF-7 cells, expressing low levels of AMPKalpha2, with stable transfection of either green fluorescent protein (GFP) or AMPKalpha2 expression constructs. AMPKalpha2 was found to be significantly suppressed in breast cancer tissue samples, whereas AMPKalpha1 was not. In normal HMECs, low glucose stress resulted in AMPK-driven growth inhibition. Interestingly, this response was ablated when AMPKalpha2 was silenced. Metabolic stress assays in MCF-7 cells indicated that AMPKalpha2 expression reduced both mTOR signaling and cyclin D1 expression, contributing to G1-phase cell cycle arrest. Cells expressing AMPKalpha2 underwent apoptosis more readily than GFP control cells. Xenograft studies demonstrated that MCF-7 tumors expressing AMPKalpha2 display reduced proliferation and increased apoptotic events.

Furthermore, AMPK α 2 xenografts exhibited diminished cyclin D1 levels along with an increased amount of nuclear p53, thereby implicating the AMPK α 2-p53 signaling axis as a mediator of cell apoptosis. Together, these results highlight the significance of reduced AMPK activity contributing to human carcinogenesis and, specifically, the role of AMPK α 2 with respect to its control of normal mammary epithelial cell growth and its reduced expression in breast cancer.

[987]

TÍTULO / TITLE: - SNP (-617C>A) in ARE-Like Loci of the NRF2 Gene: A New Biomarker for Prognosis of Lung Adenocarcinoma in Japanese Non-Smoking Women.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 11;8(9):e73794. doi: 10.1371/journal.pone.0073794.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073794](https://doi.org/10.1371/journal.pone.0073794)

AUTORES / AUTHORS: - Okano Y; Nezu U; Enokida Y; Lee MT; Kinoshita H; Lezhava A; Hayashizaki Y; Morita S; Taguri M; Ichikawa Y; Kaneko T; Natsumeda Y; Yokose T; Nakayama H; Miyagi Y; Ishikawa T

INSTITUCIÓN / INSTITUTION: - Omics Science Center, RIKEN Yokohama Institute, Yokohama, Japan ; Department of Clinical Oncology, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

RESUMEN / SUMMARY: - PURPOSE: The transcription factor NRF2 plays a pivotal role in protecting normal cells from external toxic challenges and oxidative stress, whereas it can also endow cancer cells resistance to anticancer drugs. At present little information is available about the genetic polymorphisms of the NRF2 gene and their clinical relevance. We aimed to investigate the single nucleotide polymorphisms in the NRF2 gene as a prognostic biomarker in lung cancer. EXPERIMENTAL DESIGN: We prepared genomic DNA samples from 387 Japanese patients with primary lung cancer and detected SNP (c.-617C>A; rs6721961) in the ARE-like loci of the human NRF2 gene by the rapid genetic testing method we developed in this study. We then analyzed the association between the SNP in the NRF2 gene and patients' overall survival. RESULTS: Patients harboring wild-type (WT) homozygous (c.-617C/C), SNP heterozygous (c.-617C/A), and SNP homozygous (c.-617^A/A) alleles numbered 216 (55.8%), 147 (38.0%), and 24 (6.2%), respectively. Multivariate logistic regression models revealed that SNP homozygote (c.-617^A/A) was significantly related to gender. Its frequency was four-fold higher in female patients than in males (10.8% female vs 2.7% male) and was associated with female non-smokers with adenocarcinoma. Interestingly, lung cancer patients carrying NRF2 SNP homozygous alleles (c.-617^A/A) and the 309T (WT) allele in the MDM2 gene exhibited remarkable survival over 1,700 days after surgical operation (log-rank p = 0.021). CONCLUSION: SNP homozygous (c.-617^A/A) alleles in the NRF2 gene are associated with female non-smokers with adenocarcinoma and regarded as a

prognostic biomarker for assessing overall survival of patients with lung adenocarcinoma.

[988]

TÍTULO / TITLE: - Androgen Receptor Increases CD133 Expression and Progenitor-Like Population That Associate With Cisplatin Resistance in Endometrial Cancer Cell Line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Reprod Sci.* 2013 Sep 10.

●● Enlace al texto completo (gratis o de pago) [1177/1933719113497281](https://doi.org/10.1177/1933719113497281)

AUTORES / AUTHORS: - Chen L; Chang WC; Hung YC; Chang YY; Bao BY; Huang HC; Chung WM; Shyr CR; Ma WL

INSTITUCIÓN / INSTITUTION: - 1Sex Hormone Research Center, Graduate Institution of Clinical Medical Science, School of Medicine, China Medical University, Taichung, Taiwan.

RESUMEN / SUMMARY: - Endometrial cancer (EMC) is a sex steroid hormone-related female malignancy. Androgen and androgen receptor (androgen/AR) signals have been implicated in EMC progression. Cancer stem/progenitor cells (CSPCs) are suspected to link to chemoresistance in patients with EMC. In this study, we examined the androgen/AR roles in cisplatin resistance and CSPC population. We found AR expression increased naive EMC side population, CSPC population, cell migration, and epithelial-mesenchymal transition. Meanwhile, it decreased cisplatin cytotoxic effect on EMC cells. Collaterally, endogenous AR expressions in EMC cells were upregulated in the cisplatin-resisting state. Moreover, AR expression could further enhance CD133 expression, CSPC-related markers, and drug-resistance gene messenger RNA expression in EMC cells. Finally, the AR-associated gene expression might go through indirect regulation. This is the first report revealing AR function on EMC cells' CSPC and cisplatin resistance.

[989]

TÍTULO / TITLE: - Profiles of Basal and stimulated receptor signaling networks predict drug response in breast cancer lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Sci Signal.* 2013 Sep 24;6(294):ra84. doi: 10.1126/scisignal.2004379.

●● Enlace al texto completo (gratis o de pago) [1126/scisignal.2004379](https://doi.org/10.1126/scisignal.2004379)

AUTORES / AUTHORS: - Niepel M; Hafner M; Pace EA; Chung M; Chai DH; Zhou L; Schoeberl B; Sorger PK

INSTITUCIÓN / INSTITUTION: - 1Harvard Medical School Library of Integrated Network-based Cellular Signatures Center, Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA.

RESUMEN / SUMMARY: - Identifying factors responsible for variation in drug response is essential for the effective use of targeted therapeutics. We profiled signaling pathway activity in a collection of breast cancer cell lines before and after stimulation with physiologically relevant ligands, which revealed the variability in network activity among cells of known genotype and molecular subtype. Despite the receptor-based classification of breast cancer subtypes, we found that the abundance and activity of signaling proteins in unstimulated cells (basal profile), as well as the activity of proteins in stimulated cells (signaling profile), varied within each subtype. Using a partial least-squares regression approach, we constructed models that significantly predicted sensitivity to 23 targeted therapeutics. For example, one model showed that the response to the growth factor receptor ligand heregulin effectively predicted the sensitivity of cells to drugs targeting the cell survival pathway mediated by PI3K (phosphoinositide 3-kinase) and Akt, whereas the abundance of Akt or the mutational status of the enzymes in the pathway did not. Thus, basal and signaling protein profiles may yield new biomarkers of drug sensitivity and enable the identification of appropriate therapies in cancers characterized by similar functional dysregulation of signaling networks.

[990]

TÍTULO / TITLE: - Gemcitabine eliminates double minute chromosomes from human ovarian cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 22;8(8):e71988. doi: 10.1371/journal.pone.0071988.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pone.0071988](#)

AUTORES / AUTHORS: - Yu L; Zhao Y; Quan C; Ji W; Zhu J; Huang Y; Guan R; Sun D; Jin Y; Meng X; Zhang C; Yu Y; Bai J; Sun W; Fu S

INSTITUCIÓN / INSTITUTION: - Laboratory of Medical Genetics, Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - Double minute chromosomes are cytogenetic manifestations of gene amplification frequently seen in cancer cells. Genes amplified on double minute chromosomes include oncogenes and multi-drug resistant genes. These genes encode proteins which contribute to cancer formation, cancer progression, and development of resistance to drugs used in cancer treatment. Elimination of double minute chromosomes, and therefore genes amplified on them, is an effective way to decrease the malignancy of cancer cells. We investigated the effectiveness of a cancer drug, gemcitabine, on the loss of double minute chromosomes from the ovarian cancer cell line UACC-1598. Gemcitabine is able to decrease the number of double minute chromosomes in cells at a 7500X lower concentration than the commonly used cancer drug hydroxyurea. Amplified genes present on the double minute chromosomes are decreased at the DNA level upon gemcitabine treatment. Gemcitabine, even at a low

nanomolar concentration, is able to cause DNA damage. The selective incorporation of double minutes chromatin and gamma-H2AX signals into micronuclei provides a strong link between DNA damage and the loss of double minute chromosomes from gemcitabine treated cells. Cells treated with gemcitabine also showed decreased cell growth, colony formation, and invasion. Together, our results suggest that gemcitabine is effective in decreasing double minute chromosomes and this affects the biology of ovarian cancer cells.

[991]

TÍTULO / TITLE: - High lysophosphatidylcholine acyltransferase 1 expression independently predicts high risk for biochemical recurrence in prostate cancers.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Oncol. 2013 Jul 19. pii: S1574-7891(13)00106-3. doi: 10.1016/j.molonc.2013.07.009.

●● Enlace al texto completo (gratis o de pago) 1016/j.molonc.2013.07.009

AUTORES / AUTHORS: - Grupp K; Sanader S; Sirma H; Simon R; Koop C; Prien K; Hube-Magg C; Salomon G; Graefen M; Heinzer H; Minner S; Izbicki JR; Sauter G; Schlomm T; Tsourlakis MC

INSTITUCIÓN / INSTITUTION: - General, Visceral and Thoracic Surgery Department and Clinic, University Medical Center Hamburg-Eppendorf, Germany; Institute of Pathology, University Medical Center Hamburg-Eppendorf, Germany. Electronic address: k.grupp@uke.de.

RESUMEN / SUMMARY: - Lysophosphatidylcholine acyltransferase 1 (LPCAT1) has been suggested to play a role in cancer. To assess its role in prostate cancer, LPCAT1 expression was analyzed on a tissue microarray containing samples from 11,152 prostate cancer patients. In benign prostate glands, LPCAT1 immunostaining was absent or weak. In prostate cancer, LPCAT1 positivity was found in 73.8% of 8786 interpretable tumors including 29.2% with strong expression. Increased LPCAT1 expression was associated with advanced tumor stage (pT3b/T4) ($p < 0.0001$), high Gleason score ($\geq 4 + 4$) ($p < 0.0001$), positive nodal involvement ($p = 0.0002$), positive surgical margin ($p = 0.0005$), and early PSA recurrence ($p < 0.0001$). High LPCAT1 expression was strongly linked to ERG-fusion type prostate cancer. Strong LPCAT1 staining was detected in 45.3% of ERG positive but in only 16.7% of ERG negative tumors ($p < 0.0001$). Within ERG negative cancers, LPCAT1 staining was strongly increased within the subgroup of PTEN deleted cancers ($p < 0.0001$). Further subgroup analyses revealed that associations of high LPCAT1 expression with PSA recurrence and unfavorable tumor phenotype were largely driven by ERG negative cancers ($p < 0.0001$) while these effects were substantially mitigated in ERG positive cancers ($p = 0.0073$). The prognostic impact of LPCAT1 expression was independent of histological and clinical parameters. It is concluded, that LPCAT1 measurement, either alone or in

combination, may be utilized for better clinical decision-making. These data also highlight the potentially important role of lipid metabolism in prostate cancer biology.

[992]

TÍTULO / TITLE: - Antitumor effects of mutant endostatin are enhanced by Bcl-2 antisense oligonucleotides in UM-UC-3 bladder cancer cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chin Med J (Engl). 2013;126(15):2834-9.

AUTORES / AUTHORS: - Ren MH; Yu JS; Song EL; Zhang C; Ma L; Jiao ZX; Zhao WM; Shan YJ; Ni SB

RESUMEN / SUMMARY: - BACKGROUND: Endostatin is a potent inhibitor of tumor angiogenesis. In the preliminary studies, we developed a mutant endostatin containing Arg-Gly-Asp-Arg-Gly-Asp (RGDRGD) sequences. In this study, we compared the antitumor effects of mutant endostatin and Bcl-2 antisense oligonucleotides both in combination and individually. METHODS: The artificially synthesized Bcl-2 ASODN (antisense oligonucleotides) included a translation-initiation site and was transfected into the bladder cancer cells by Lipofectamine. Cell growth was investigated by the tumor cell growth chart, MTT assay, caspase-3 activity detection assay, AO/EB fluorescein stain, and the annexin V-FITC apoptosis detection assay. In the in vivo study, UM-UC-3 bladder cancer cells were subcutaneously implanted into nude mice and the growth of tumor was examined. The ultrastructure of the tumor tissues in the treated and control groups were observed. RESULTS: The cell growth chart showed that the cell population of the treated combination group decreased by 52.04% compared to the control group. The inhibition rate of the treated combination group was (79.66 +/- 6.79)%, whereas those of the individual ASODN and ES groups were (53.39 +/- 3.22)% and (50.22 +/- 5.46)% respectively. In the caspase-3 activity detection using AO/EB fluorescein stain and annexin V-FITC apoptosis detection assay, the co-inhibitory effect was higher than the individual inhibitory effects (P < 0.05). There were significant differences in the inhibition of the solid tumor growth in the in vivo study. CONCLUSIONS: Our findings indicated that Bcl-2 antisense oligonucleotides enhance the antitumor effects of mutant endostatin both in vitro and in vivo. We noted the synergistic effects of Bcl-2 antisense oligonucleotides combined with mutant endostatin.

[993]

TÍTULO / TITLE: - Combination of siRNA-directed Kras oncogene silencing and arsenic-induced apoptosis using a nanomedicine strategy for the effective treatment of pancreatic cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nanomedicine. 2013 Sep 9. pii: S1549-9634(13)00469-3. doi: 10.1016/j.nano.2013.08.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.nano.2013.08.007](https://doi.org/10.1016/j.nano.2013.08.007)

AUTORES / AUTHORS: - Zeng L; Li J; Wang Y; Qian C; Chen Y; Zhang Q; Wu W; Lin Z; Liang J; Shuai X; Huang K

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, The Second Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Department of Oncology, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China.

RESUMEN / SUMMARY: - The synergetic inhibitory effects on human pancreatic cancer by nanoparticle-mediated siRNA and arsenic therapy were investigated both in vitro and in vivo. Poly(ethylene glycol)-block-poly(L-lysine) were prepared to form siRNA-complexed polyplex and poly(ethylene glycol)-block-poly(DL-lactide) were prepared to form arsenic-encapsulated vesicle, respectively. Down-regulation of the mutant Kras gene by siRNA caused defective abilities of proliferation, clonal formation, migration, and invasion of pancreatic cancer cells, as well as cell cycle arrest at the G0/G1 phase, which substantially enhanced the apoptosis-inducing effect of arsenic administration. Consequently, co-administration of the two nanomedicines encapsulating siRNA or arsenic showed ideal tumor growth inhibition both in vitro and in vivo as a result of synergistic effect of the siRNA-directed Kras oncogene silencing and arsenic-induced cell apoptosis. These results suggest that the combination of mutant Kras gene silencing and arsenic therapy using nanoparticle-mediated delivery strategy is promising for pancreatic cancer treatment.

[994]

TÍTULO / TITLE: - Changes in molecular biology of chronic myeloid leukemia in tyrosine kinase inhibitor era.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Am J Blood Res. 2013 Aug 19;3(3):191-200.

AUTORES / AUTHORS: - Comert M; Baran Y; Saydam G

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Medical School, Ege University Izmir, Turkey.

RESUMEN / SUMMARY: - Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease characterized by a reciprocal translocation between long arms of chromosomes 9 and 22 t(9;22) that generates the BCR-ABL fusion gene. If left untreated, newly diagnosed chronic phase CML patients finally progress to accelerated and blastic phase. After the introduction of tyrosine kinase inhibitors (TKIs), treatment strategies of CML changed dramatically. However, the development of resistance to TKIs started to create problems over time. In this review, the current information about CML biology before and after imatinib mesylate treatment is summarized.

[995]

TÍTULO / TITLE: - The role of interleukin-6 in the evolution of ovarian cancer: clinical and prognostic implications-a review.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Med (Berl). 2013 Sep 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00109-013-1080-7](#)

AUTORES / AUTHORS: - Maccio A; Madeddu C

INSTITUCIÓN / INSTITUTION: - Department of Gynecologic Oncology, "A. Businco" Hospital, Regional Referral Center for Cancer Disease, via Edward Jenner, 09121, Cagliari, Italy, a.maccio@tin.it.

RESUMEN / SUMMARY: - An increasing number of studies emphasize the role of inflammation and metabolic changes in the induction of cancer-related symptoms, which can affect cancer evolution and prognosis. These changes result from the interactions between the tumor and the host. To date, however, markers of this peculiar condition, which can help clinicians to manage patients better, have still not been identified with certainty. Epithelial ovarian cancer (EOC) appears to be particularly appropriate to study these interactions because of its biological characteristics, its peculiar evolution, and the relevant scientific evidence available. Immunosuppression, anemia, depression, and weight loss affect the evolution of EOC and appear to be directly related to the immune-metabolic changes. In light of the aforementioned evidence, our review will focus on interleukin-6 (IL-6) and its role as potential marker of the patients' immune-metabolic status, to better monitor disease outcome and identify the most appropriate therapeutic strategy in EOC. Furthermore, leptin will be discussed as a sensor of the changes of energy metabolism induced by IL-6.

[996]

TÍTULO / TITLE: - Clinicopathological features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Hepatobiliary Pancreat Sci. 2013 Aug 1. doi: 10.1002/jhbp.23.

●● Enlace al texto completo (gratis o de pago) [1002/jhbp.23](#)

AUTORES / AUTHORS: - Kubota K; Nakanuma Y; Kondo F; Hachiya H; Miyazaki M; Nagino M; Yamamoto M; Isayama H; Tabata M; Kinoshita H; Kamisawa T; Inui K

INSTITUCIÓN / INSTITUTION: - Second Department of Surgery, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0283, Japan. kubotak@dokkyomed.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: The aim of this study was to determine the clinicopathological features and surgical outcomes of mucinous cystic neoplasm of the liver (MCN) and mucin-producing intrahepatic biliary neoplasm of the intrahepatic bile duct (M-IPNB). METHODS: We performed a multi-institutional, retrospective study of patients with MCN or M-IPNB pathologically defined by the presence or absence of

an ovarian-like stroma. RESULTS: The M-IPNB and MCN were diagnosed in 119 and nine patients, respectively. MCN was observed in female patients, while M-IPNB produced symptoms of cholangitis. M-IPNBs were classed as low or intermediate grade in 53 cases, high grade in 23 and invasive carcinoma in 43. Fifty-one of the M-IPNBs were the pancreatobiliary type (PT), 33 were the intestinal type (IT), 23 were the oncocytic type (OT), and 12 were the gastric type (GT). The 1-, 5- and 10-year survival rates for the 105 patients with M-IPNB were 96%, 84% and 81%, respectively, while the 5-year survival rate for patients with MCN was 100%. OT and GT M-IPNB had better 10-year survival rates than PT and IT M-IPNB. CONCLUSIONS: Although MCN has different features from M-IPNB, both diseases have a good prognosis after resection. The cellular type of M-IPNB appears to predict outcome.

[997]

TÍTULO / TITLE: - Phosphorylation of estrogen receptor alpha at serine 118 is correlated with breast cancer resistance to tamoxifen.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2013 Jul;6(1):118-124. Epub 2013 Apr 29.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1324](#)

AUTORES / AUTHORS: - Chen M; Cui YK; Huang WH; Man K; Zhang GJ

INSTITUCIÓN / INSTITUTION: - Breast Center of The Affiliated Cancer Hospital of Shantou University Medical College, Shantou, Guangdong 515031; ; Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730;

RESUMEN / SUMMARY: - The aim of the present study was to explore the correlation between estrogen receptor alpha (ERalpha) phosphorylation at serines 118 and 167 and the responsiveness of patients with primary breast cancer to tamoxifen. Tumors from 104 patients with primary breast cancer who received adjuvant tamoxifen therapy at The Affiliated Cancer Hospital of Shantou University Medical College between January 2001 to December 2007 were subjected to immunohistochemical analysis with specific antibodies against ERalpha phosphorylated at either serine 118 (pERalpha-S118) and/or serine 167 (pERalpha-S167). ERalpha phosphorylation at the two sites was correlated with either the disease-free survival or the overall survival rate of these patients using the Kaplan-Meier survival analysis. pERalpha-S118 and pERalpha-S167 were found to be expressed in the cell nucleus of 25.0% (26/104) and 26.9% (28/104) of breast cancers, respectively. The expression of pERalpha-S118 was positively correlated with the human epidermal growth factor receptor-2 (HER-2) status ($\chi^2=6.85$, $P=0.01$). The Kaplan-Meier analysis revealed a poorer disease-free ($P=0.022$) and overall survival ($P=0.013$) in breast cancer patients expressing pERalpha-S118, but not in those expressing pERalpha-S167. In conclusion, pERalpha-S118 was correlated with the HER-2 status and predicted breast cancer resistance to tamoxifen.

[998]

TÍTULO / TITLE: - A miniaturized chemical proteomic approach for target profiling of clinical kinase inhibitors in tumor biopsies.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Proteome Res. 2013 Sep 6;12(9):4005-17. doi: 10.1021/pr400309p. Epub 2013 Aug 20.

●● Enlace al texto completo (gratis o de pago) [1021/pr400309p](#)

AUTORES / AUTHORS: - Chamrad I; Rix U; Stukalov A; Gridling M; Parapatits K; Muller AC; Altiok S; Colinge J; Superti-Furga G; Haura EB; Bennett KL

INSTITUCIÓN / INSTITUTION: - Department of Protein Biochemistry and Proteomics, Technological Centre of the Palacky University, Centre of the Region Hana for Biotechnological and Agricultural Research, Olomouc, Czech Republic.

RESUMEN / SUMMARY: - While targeted therapy based on the idea of attenuating the activity of a preselected, therapeutically relevant protein has become one of the major trends in modern cancer therapy, no truly specific targeted drug has been developed and most clinical agents have displayed a degree of polypharmacology. Therefore, the specificity of anticancer therapeutics has emerged as a highly important but severely underestimated issue. Chemical proteomics is a powerful technique combining postgenomic drug-affinity chromatography with high-end mass spectrometry analysis and bioinformatic data processing to assemble a target profile of a desired therapeutic molecule. Due to high demands on the starting material, however, chemical proteomic studies have been mostly limited to cancer cell lines. Herein, we report a down-scaling of the technique to enable the analysis of very low abundance samples, as those obtained from needle biopsies. By a systematic investigation of several important parameters in pull-downs with the multikinase inhibitor bosutinib, the standard experimental protocol was optimized to 100 µg protein input. At this level, more than 30 well-known targets were detected per single pull-down replicate with high reproducibility. Moreover, as presented by the comprehensive target profile obtained from miniaturized pull-downs with another clinical drug, dasatinib, the optimized protocol seems to be extendable to other drugs of interest. Sixty distinct human and murine targets were finally identified for bosutinib and dasatinib in chemical proteomic experiments utilizing core needle biopsy samples from xenotransplants derived from patient tumor tissue. Altogether, the developed methodology proves robust and generic and holds many promises for the field of personalized health care.

[999]

TÍTULO / TITLE: - Pharmacogenetic considerations for non-Hodgkin's lymphoma therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Opin Drug Metab Toxicol. 2013 Sep 22.

●● Enlace al texto completo (gratis o de pago) [1517/17425255.2013.835803](#)

AUTORES / AUTHORS: - Espirito-Santo A; Medeiros R

INSTITUCIÓN / INSTITUTION: - Servicio de OncoHematología, Portuguese Institute of Oncology , Porto , Portugal.

RESUMEN / SUMMARY: - Introduction: Chemotherapy is the current standard treatment for hematological malignancies for both curative and palliative purposes. Unfortunately, in the current treatment scenario chemotherapy resistance is an issue that is known to lead to a relapse in cancer. The multidrug resistance 1 (MDR1) gene is often involved in drug resistance and, so far, the best studied mechanism of resistance relates to the level of P-glycoprotein (P-gp) expression on cancer cells; however, correlation with single nucleotide polymorphism (SNP) in the MDR1 gene has also been observed via a number of different mechanisms that interfere with function and expression of P-gp. Areas covered: This article describes the influence of P-gp expression and SNP on the MDR1 gene in non-Hodgkin's lymphoma (NHL) and their effect on both its risk and outcome. The authors also provide a brief summary of the more important therapeutic options, which aim to overcome this drug resistance mechanism, and discuss their known mechanisms of action. Expert opinion: There is evidence pertaining to an association between the outcome of NHL and P-gp expression. However, the authors emphasize the need for more studies to reinforce this evidence. Furthermore, there is a definite need for the therapeutic targets, which provide tumor cellular lines of interest, to be tested in humans, in order to better evaluate their toxicity and overall effect on the outcome. The ultimate aim of this research is to develop specifically designed therapies that are tailored to the intrinsic characteristics of specific patients.

Expert Opin Drug Metab Toxicol -----
----- [1000]

TÍTULO / TITLE: - The marine natural product manzamine targets vacuolar ATPases and inhibits autophagy in pancreatic cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mar Drugs. 2013 Sep 17;11(9):3500-16. doi: 10.3390/md11093500.

●● Enlace al texto completo (gratis o de pago) [3390/md11093500](#)

AUTORES / AUTHORS: - Kallifatidis G; Hoepfner D; Jaeg T; Guzman EA; Wright AE

INSTITUCIÓN / INSTITUTION: - Marine Biomedical and Biotechnology Research Program, Harbor Branch Oceanographic Institute, Florida Atlantic University, 5600 US 1 North, Fort Pierce, FL 34946, USA. eguzman9@hboi.fau.edu.

RESUMEN / SUMMARY: - Manzamine A, a member of the manzamine alkaloids, was originally isolated from marine sponges of the genus Haliclona. It was recently shown to have activity against pancreatic cancer cells, but the precise mechanism of action remained unclear. To further our understanding of the mechanism of action of manzamine A, chemogenomic profiling in the yeast *S. cerevisiae* was performed, suggesting that manzamine A is an uncoupler of vacuolar ATPases. Fluorescence microscopy confirmed this effect on yeast vacuoles, where manzamine A produced a phenotype very similar to that of the established v-ATPase inhibitor bafilomycin A1. In

pancreatic cancer cells, 10 microM manzamine A affected vacuolar ATPase activity and significantly increased the level of autophagosome marker LC3-II and p62/SQSTM1 as observed by western blot analysis. Treatment with manzamine A in combination with bafilomycin A1 (inhibitor of autophagosome-lysosome fusion) did not change the levels of LC3-II when compared to cells treated with bafilomycin A1 alone, suggesting that manzamine A is a potential inhibitor of autophagy by preventing autophagosome turnover. As autophagy is essential for pancreatic tumor growth, blocking this pathway with manzamine A suggests a promising strategy for the treatment of pancreatic cancer.

[1001]

TÍTULO / TITLE: - Nemo-like kinase associated with proliferation and apoptosis by c-Myb degradation in breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e69148. doi: 10.1371/journal.pone.0069148. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069148](#)

AUTORES / AUTHORS: - Huang Y; Jiang Y; Lu W; Zhang Y

INSTITUCIÓN / INSTITUTION: - Department of Tumor Chemotherapy, Affiliated Hospital of Nantong University, Medical College, Nantong University, Nantong, Jiangsu, China.

RESUMEN / SUMMARY: - Nemo-like kinase (NLK), a mediator of the Wnt signaling pathway, binds directly to c-Myb, leading to its phosphorylation, ubiquitination and proteasome-dependent degradation. NLK was significantly downregulated in the breast cancer tissues compared to corresponding normal tissues. NLK expression was negatively correlated with c-Myb expression. NLK suppressed proliferation, induced apoptosis and mediated c-Myb degradation in MCF-7 cells via a mechanism that seems to involve c-myc and Bcl2. These findings might provide a novel target for therapeutic intervention in patients with breast cancer.

[1002]

TÍTULO / TITLE: - Doxorubicin-loaded amphiphilic polypeptide-based nanoparticles as an efficient drug delivery system for cancer therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Biomater. 2013 Aug 17. pii: S1742-7061(13)00407-8. doi: 10.1016/j.actbio.2013.08.015.

●● Enlace al texto completo (gratis o de pago) [1016/j.actbio.2013.08.015](#)

AUTORES / AUTHORS: - Lv S; Li M; Tang Z; Song W; Sun H; Liu H; Chen X

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China; University of Chinese Academy of Sciences, Beijing 100039, China.

RESUMEN / SUMMARY: - An amphiphilic anionic copolymer, methoxy poly(ethylene glycol)-b-poly(L-glutamic acid-co-L-phenylalanine) (mPEG-b-P(Glu-co-Phe)), with three functionalized domains, was synthesized and used as a nanovehicle for cationic anticancer drug doxorubicin hydrochloride (DOX.HCl) delivery via electrostatic interactions for cancer treatment. The three domains displayed distinct functions: PEG block chain for prolonged circulation; poly(phenylalanine) domain for stabilizing the nanoparticle construct through hydrophobic/aromatic interactions; and the poly(glutamic acid) domain for providing electrostatic interactions with the cationic drug to be loaded. The copolymer could self-assemble into micellar-type nanoparticles, and DOX was successfully loaded into the interior of nanoparticles by simple mixing of DOX.HCl and the copolymer in the aqueous phase. DOX-loaded mPEG-b-P(Glu-co-Phe) nanoparticles (DOX-NP) had a superior drug-loading content (DLC) (21.7%), a high loading efficiency (almost 98%) and a pH-triggered release of DOX. The size of DOX-NP was approximately 140nm, as determined by dynamic light scattering measurements and transmission electron microscopy. In vitro assays showed that DOX-NP exhibited higher cell proliferation inhibition and higher cell uptake in A549 cell lines compared with free DOX.HCl. Maximum tolerated dose (MTD) studies showed that DOX-NP demonstrated an excellent safety profile with a significantly higher MTD (15mg DOX kg⁻¹) than that of free DOX.HCl (5mg DOX kg⁻¹). The in vivo studies on the subcutaneous non-small cell lung cancer (A549) xenograft nude mice model confirmed that DOX-NP showed significant antitumor activity and reduced side effects, and then enhanced tumor accumulation as a result of the prolonged circulation in blood and the enhanced permeation and retention effect, compared with free DOX, indicating its great potential for cancer therapy.

[1003]

TÍTULO / TITLE: - Synthesis of glycyrrhetic Acid-modified chitosan 5-Fluorouracil nanoparticles and its inhibition of liver cancer characteristics in vitro and in vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mar Drugs. 2013 Sep 17;11(9):3517-36. doi: 10.3390/md11093517.

●● Enlace al texto completo (gratis o de pago) [3390/md11093517](#)

AUTORES / AUTHORS: - Cheng M; Gao X; Wang Y; Chen H; He B; Xu H; Li Y; Han J; Zhang Z

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Pudong New Area District Zhoupu Hospital, Shanghai 201318, China. wangyong@whut.edu.cn.

RESUMEN / SUMMARY: - Nanoparticle drug delivery (NDDS) is a novel system in which the drugs are delivered to the site of action by small particles in the nanometer range. Natural or synthetic polymers are used as vectors in NDDS, as they provide targeted, sustained release and biodegradability. Here, we used the chitosan and hepatoma cell-specific binding molecule, glycyrrhetic acid (GA), to synthesize glycyrrhetic acid-modified chitosan (GA-CTS). The synthetic product was confirmed by Fourier transformed infrared spectroscopy (FT-IR) and ¹H-nuclear magnetic resonance (¹H-

NMR). By combining GA-CTS and 5-FU (5-fluorouracil), we obtained a GA-CTS/5-FU nanoparticle, with a particle size of 217.2 nm, a drug loading of 1.56% and a polydispersity index of 0.003. The GA-CTS/5-FU nanoparticle provided a sustained release system comprising three distinct phases of quick, steady and slow release. We demonstrated that the nanoparticle accumulated in the liver. In vitro data indicated that it had a dose- and time-dependent anti-cancer effect. The effective drug exposure time against hepatic cancer cells was increased in comparison with that observed with 5-FU. Additionally, GA-CTS/5-FU significantly inhibited the growth of drug-resistant hepatoma, which may compensate for the drug-resistance of 5-FU. In vivo studies on an orthotopic liver cancer mouse model demonstrated that GA-CTS/5-FU significantly inhibited tumor growth, resulting in increased survival time.

[1004]

TÍTULO / TITLE: - Steroidal Cardiac Na⁺/K⁺ ATPase Inhibitors Exhibit Strong Anti-Cancer Potential in Vitro and in Prostate and Lung Cancer Xenografts in Vivo.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Anticancer Agents Med Chem. 2013 Sep 23.

AUTORES / AUTHORS: - Dimas K; Papadopoulou N; Baskakis C; Prousis KC; Tsakos M; Alkahtani S; Honisch S; Lang F; Calogeropoulou T; Alevizopoulos K; Stournaras C

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RESUMEN / SUMMARY: - Sodium potassium pump (Na⁺/K⁺ ATPase) is a validated pharmacological target for the treatment of congestive heart failure. Recent data with inotropic drugs such as digoxin & digitoxin (digitalis) suggest a potent anti-cancer action of these drugs and promote Na⁺/K⁺ ATPase as a novel therapeutic target in cancer. However, digitalis have narrow therapeutic indices, are pro-arrhythmic and are considered non-developable drugs by the pharmaceutical industry. On the contrary, a series of recently-developed steroidal inhibitors showed better pharmacological properties and clinical activities in cardiac patients. Their anti-cancer activity however, remained unknown. In this study, we synthesized seventeen steroidal cardiac inhibitors and explored for the first time their anti-cancer activity in vitro and in vivo. Our results indicate potent anti-cancer actions of steroidal cardiac inhibitors in multiple cell lines from different tumor panels including multi-drug resistant cells. Furthermore, the most potent compound identified in our studies, the 3-[[®]-3-pyrrolidinyl]oxime derivative 3, showed outstanding potencies (as measured by GI50, TGI and LC50 values) in most cells in vitro, was selectively cytotoxic in cancer versus normal cells showing a therapeutic index of 31.7 and exhibited significant tumor growth inhibition in prostate and lung xenografts in vivo. Collectively, our results suggest that previously described cardiac Na⁺/K⁺ ATPase inhibitors have potent anti-

cancer actions and may thus constitute strong re-purposing candidates for further cancer drug development.

[1005]

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Rom J Morphol Embryol. 2013;54(3):519-30.

AUTORES / AUTHORS: - Barbu I; Craioiu S; Simionescu CE; Dragnei AM; Margaritescu C

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, Romania; c_margaritescu2000@yahoo.com.

RESUMEN / SUMMARY: - In this study, we have investigated the immunohistochemical expression of endoglin (CD105), vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR-1) and epidermal growth factor receptor 2 (c-erbB-2) and their prognostic correlation in 13 cases of cervical adenocarcinomas with mucinous, endometrioid and serous type differentiation. Our study revealed that for uterine cervix adenocarcinoma the most intense angiogenic activity occurs at the invasion front of these tumors. In addition, we noticed a trend towards increased CD105 MVD values in those cases in which were recorded the highest VEGF and c-erbB-2 reactivity. Thus, we concluded that in cervical adenocarcinomas occurs an intense process of angiogenesis, mainly at the invasion front, controlled by interrelations between VEGF and EGFR family members, especially the c-erbB-2 receptor. Further studies are needed to elucidate whether specific angiogenic molecular profiles exist in different histopathological subtypes of uterine adenocarcinomas and which is their impact on prognosis and therapeutic outcomes for these patients.

[1006]

TÍTULO / TITLE: - 15-hydroxyprostaglandin dehydrogenase in colorectal mucosa as a potential biomarker for predicting colorectal neoplasms.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Korean Med Sci. 2013 Aug;28(8):1154-60. doi: 10.3346/jkms.2013.28.8.1154. Epub 2013 Jul 31.

●● [Enlace al texto completo \(gratis o de pago\) 3346/jkms.2013.28.8.1154](#)

AUTORES / AUTHORS: - Lee HJ; Yang DH; Ryu YM; Song M; Song HJ; Jung KW; Kim KJ; Byeon JS; Choi EK; Yang SK; Kim JH; Myung SJ

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - 15-Hydroxyprostaglandin dehydrogenase (15-PGDH) is downregulated during the early stages of colorectal carcinogenesis. The aim of the present study was to investigate the potential role of 15-PGDH in normal-appearing colorectal mucosa as a biomarker for predicting colorectal neoplasms. We obtained

paired tumor and normal tissues from the surgical specimens of 32 sporadic colorectal cancer patients. mRNA expression of 15-PGDH was measured using a quantitative real-time PCR assay. We evaluated the association between 15-PGDH mRNA expression in normal-appearing mucosa, the presence of synchronous adenoma, and the cumulative incidence of metachronous adenoma. The relative 15-PGDH expression of normal-appearing mucosa in patients with synchronous adenoma was significantly lower than in patients without synchronous adenoma (0.71 vs 1.00, $P = 0.044$). The patients in the lowest tertile of 15-PGDH expression in normal-appearing mucosa were most likely to have synchronous adenoma (OR: 10.5, $P = 0.024$). Patients with low 15-PGDH expression in normal-appearing mucosa also demonstrated more advanced stage colorectal cancer ($P = 0.045$). However, there was no significant difference in the cumulative incidence of metachronous adenoma according to 15-PGDH mRNA expression in normal-appearing mucosa ($P = 0.333$). Hence, 15-PGDH in normal-appearing colorectal mucosa can be a useful biomarker of field effect for the prediction of sporadic synchronous neoplasms.

[1007]

TÍTULO / TITLE: - Selective growth inhibition of human malignant melanoma cells by syringic acid-derived proteasome inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Aug 19;13(1):82. doi: 10.1186/1475-2867-13-82.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-82](#)

AUTORES / AUTHORS: - Orabi KY; Abaza MS; El Sayed KA; Elnagar AY; Al-Attayah R; Guleri RP

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Health Sciences Center, Kuwait University, Safat 13110, Kuwait.
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RESUMEN / SUMMARY: - BACKGROUND: It has been shown that proteasome inhibition leads to growth arrest in the G1 phase of the cell cycle and/or induction of apoptosis. However, it was found that some of these inhibitors do not induce apoptosis in several human normal cell lines. This selective activity makes proteasome inhibition a promising target for new generation of anticancer drugs. Clinical validation of the proteasome, as a therapeutic target in oncology, has been provided by the dipeptide boronic acid derivative; bortezomib. Bortezomib has proven to be effective as a single agent in multiple myeloma and some forms of non-Hodgkin's lymphoma. Syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid, 1), a known phenolic acid, was isolated from the methanol extract of *Tamarix aucheriana* and was shown to possess proteasome inhibitory activity. METHODS: Using Surflex-Dock program interfaced with SYBYL, the docking affinities of syringic acid and its proposed derivatives to 20S proteasome were

studied. Several derivatives were virtually proposed, however, five derivatives: benzyl 4-hydroxy-3,5-dimethoxybenzoate (2), benzyl 4-(benzyloxy)-3,5-dimethoxybenzoate (3), 3'-methoxybenzyl 3,5-dimethoxy-4-(3'-methoxybenzyloxy)benzoate (4), 3'-methoxybenzyl 4-hydroxy-3,5-dimethoxybenzoate (5) and 3',5'-dimethoxybenzyl 4-hydroxy-3,5-dimethoxybenzoate (6), were selected based on high docking scores, synthesized, and tested for their anti-mitogenic activity against human colorectal, breast and malignant melanoma cells as well as normal human fibroblast cells. RESULTS: Derivatives 2, 5, and 6 showed selective dose-dependent anti-mitogenic effect against human malignant melanoma cell lines HTB66 and HTB68 with minimal cytotoxicity on colorectal and breast cancer cells as well as normal human fibroblast cells. Derivatives 2, 5 and 6 significantly ($p \leq 0.0001$) inhibited the various proteasomal chymotrypsin, PGPH, and trypsin like activities. They growth arrested the growth of HTB66 cells at G1 and G2-phases. They also arrested the growth of HTB68 cells at S- and G2-phase, respectively. Moreover, derivatives 2, 5, and 6 markedly induced apoptosis ($\geq 90\%$) in both HTB66 and HTB68. CONCLUSIONS: Computer-derived syringic acid derivatives possess selective anti-mitogenic activity on human malignant melanoma cells that may be attributed to perturbation of cell cycle, induction of apoptosis and inhibition of various 26S proteasomal activities.

[1008]

TÍTULO / TITLE: - Suberoylanilide hydroxamic acid (SAHA) causes tumor growth slowdown and triggers autophagy in glioblastoma stem cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Autophagy. 2013 Aug 15;9(10).

AUTORES / AUTHORS: - Chiao MT; Cheng WY; Yang YC; Shen CC; Ko JL

INSTITUCIÓN / INSTITUTION: - Institute of Medicine; Chung Shan Medical University; Taichung, Taiwan; Institute of Medical and Molecular Toxicology; Chung Shan Medical University; Taichung, Taiwan.

RESUMEN / SUMMARY: - Although suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, has been used in clinical trials for cancer therapies, its pharmacological effects occur through a poorly understood mechanism. Here, we report that SAHA specifically triggers autophagy and reduces cell viability via promotion of apoptosis in the late phase of glioblastoma stem cells (GSCs). Using a cell line cultured from a glioblastoma biopsy, we investigated the properties and effects of GSCs under SAHA treatment in vitro. In vivo xenograft assays revealed that SAHA effectively caused tumor growth slowdown and the induction of autophagy. SAHA was sufficient to increase formation of intracellular acidic vesicle organelles, recruitment of LC3-II to the autophagosomes, potentiation of BECN1 protein levels and reduced SQSTM1 levels. We determined that SAHA triggered autophagy through the downregulation of AKT-MTOR signaling, a major suppressive cascade of autophagy. Interestingly, upon depletion or pharmacological inhibition of autophagy, SAHA

facilitates apoptosis and results in cell death at the early phase, suggesting that SAHA-induced autophagy functions probably act as a prosurvival mechanism. Furthermore, our results also indicated that the inhibition of SAHA-induced autophagy using chloroquine has synergistic effects that further increase apoptosis. Moreover, we found that a reduced dose of SAHA functioned as a potent modulator of differentiation and senescence. Taken together, our results provide a new perspective on the treatment of GSCs, indicating that SAHA is a promising agent for targeting GSCs through the induction of autophagy.

[1009]

TÍTULO / TITLE: - The effects of high concentrations of vitamin C on cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nutrients. 2013 Sep 9;5(9):3496-505. doi: 10.3390/nu5093496.

●● Enlace al texto completo (gratis o de pago) [3390/nu5093496](#)

AUTORES / AUTHORS: - Park S

INSTITUCIÓN / INSTITUTION: - Department of Applied Chemistry, Dongduk Women's University, 23-1 Wolgok-dong, Sungbuk-ku, Seoul 136-714, Korea.

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RESUMEN / SUMMARY: - The effect of high doses of vitamin C for the treatment of cancer has been controversial. Our previous studies, and studies by others, have reported that vitamin C at concentrations of 0.25-1.0 mM induced a dose- and time-dependent inhibition of proliferation in acute myeloid leukemia (AML) cell lines and in leukemic cells from peripheral blood specimens obtained from patients with AML. Treatment of cells with high doses of vitamin C resulted in an immediate increase in intracellular total glutathione content and glutathione-S transferase activity that was accompanied by the uptake of cysteine. These results suggest a new role for high concentrations of vitamin C in modulation of intracellular sulfur containing compounds, such as glutathione and cysteine. This review, discussing biochemical pharmacologic studies, including pharmacogenomic and pharmacoproteomic studies, presents the different pharmacological effects of vitamin C currently under investigation.

[1010]

TÍTULO / TITLE: - Tyrosyl-DNA phosphodiesterase 1 (TDP1) and Poly (ADP-Ribose) Polymerase-1 (PARP1) deficiency are cytotoxic to rhabdomyosarcoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Res. 2013 Aug 2.

●● Enlace al texto completo (gratis o de pago) [1158/1541-7786.MCR-12-](#)

[0575](#)

AUTORES / AUTHORS: - Fam HK; Walton C; Mitra SA; Chowdhury M; Osborne N; Choi K; Sun G; Wong PC; O'Sullivan MJ; Turashvili G; Aparicio S; Triche TJ; Bond M; Pallen CJ; Boerkoel CF 3rd

INSTITUCIÓN / INSTITUTION: - University of British Columbia.

RESUMEN / SUMMARY: - Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. Children with metastatic RMS have a five-year event-free survival of <30% and a recent trial of the topoisomerase I inhibitor irinotecan failed to improve outcome. We hypothesized that this resistance to irinotecan arose from overexpression of the DNA repair enzyme tyrosyl-DNA phosphodiesterase (Tdp1) which processes topoisomerase I-DNA complexes resulting from topoisomerase I inhibitor treatment. Using tissue microarrays and gene expression arrays, we found marked overexpression of Tdp1 protein and mRNA in RMS tumors and that knockdown of TDP1 or inhibition of poly (ADP-ribose) polymerase-1 (PARP-1), an enzyme in the same complex as Tdp1, sensitized RMS cell lines to analogues of irinotecan. Interestingly, although BRCA1 and BRCA2 mutations or altered expression were undetectable in RMS cell lines, TDP1 knockdown and PARP-1 inhibition alone were cytotoxic to some RMS cells suggesting that they harbor genetic lesions of DNA repair that have synthetic lethal interactions with loss of Tdp1 or PARP1 function. Furthermore, culturing embryonal RMS cells in low-serum, low-glucose medium increased cytotoxicity of PARP-1 inhibition and was intrinsically cytotoxic to alveolar, though not embryonal RMS cells. We conclude therefore that TDP1 knockdown, PARP-1 inhibition and dietary restriction are considerations as components of RMS therapies.

[1011]

TÍTULO / TITLE: - Marchantin M: a novel inhibitor of proteasome induces autophagic cell death in prostate cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 8;4:e761. doi: 10.1038/cddis.2013.285.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.285](#)

AUTORES / AUTHORS: - Jiang H; Sun J; Xu Q; Liu Y; Wei J; Young CY; Yuan H; Lou H

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Shandong University School of Medicine, Jinan 250012, China.

RESUMEN / SUMMARY: - We previously reported that marchantin M (Mar) is an active agent to induce apoptosis in human prostate cancer (PCa), but the molecular mechanisms of action remain largely unknown. Here, we demonstrate that Mar potently inhibited chymotrypsin-like and peptidyl-glutamyl peptide-hydrolyzing activities of 20S proteasome both in in vitro and intracellular systems and significantly induced the accumulation of polyubiquitinated proteins in PCa cells. The computational modeling analysis suggested that Mar non-covalently bound to active sites of proteasome beta5 and beta1 subunits, resulting in a non-competitive inhibition. Proteasome inhibition by Mar subsequently resulted in endoplasmic reticulum (ER) stress, as evidenced by elevated glucose-regulated protein 78 and CHOP, increased phospho-eukaryotic translation initiation factor 2alpha (eIF(2alpha)),

splicing of X-box-binding protein-1 and dilation of the ER. However, Mar-mediated cell death was not completely impaired by a pan inhibitor of caspases. Further studies revealed that the Mar-induced cell death was greatly associated with the activation of autophagy, as indicated by the significant induction of microtubule-associated protein-1 light chain-3 beta (LC3B) expression and conversion. Electron microscopic and green fluorescent protein-tagged LC3B analyses further demonstrated the ability of autophagy induction by Mar. Time kinetic studies revealed that Mar induced a rapid and highly sustained processing of LC3B in treated cells and simultaneously decreased the expression of p62/SQSTM1. Pharmacological blockade or knockdown of LC3B and Atg5 attenuated Mar-mediated cell death. The autophagic response triggered by Mar required the activation of RNA-dependent protein kinase-like ER kinase/eIF(2alpha) and suppression of the phosphatidylinositol-3 kinase/Akt/mammalian target of rapamycin axis via preventing activation and expression of Akt. Our results identified a novel mechanism for the cytotoxic effect of Mar, which strengthens it as a potential agent in cancer chemotherapy.

[1012]

TÍTULO / TITLE: - Loss of PI(4,5)P2 5-Phosphatase A Contributes to Resistance of Human Melanoma Cells to RAF/MEK Inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Transl Oncol. 2013 Aug 1;6(4):470-81. Print 2013 Aug.

AUTORES / AUTHORS: - Ye Y; Li Q; Hu WL; Tseng HY; Jin L; Zhang XD; Zhang LJ; Yang S

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Anhui Medical University, Anhui, China.

RESUMEN / SUMMARY: - Past studies have shown that the inositol polyphosphate 5-phosphatase, phosphatidylinositol 4,5-bisphosphate 5-phosphatase (PIB5PA), is commonly downregulated or lost in melanomas, which contributes to elevated activation of phosphatidylinositol 3-kinase (PI3K)/Akt in melanoma cells. In this report, we provide evidence that PIB5PA deficiency plays a role in resistance of melanoma cells to RAF/mitogen-activated protein kinase kinase (MEK) inhibitors. Ectopic expression of PIB5PA enhanced apoptosis induced by the RAF inhibitor PLX4720 in BRAF(V600E) and by the MEK inhibitor U0126 in both BRAF(V600E) and wild-type BRAF melanoma cells. This was due to inhibition of PI3K/Akt, as co-introduction of an active form of Akt (myr-Akt) abolished the effect of overexpression of PIB5PA on apoptosis induced by PLX4720 or U0126. While overexpression of PIB5PA triggered activation of Bad and down-regulation of Mcl-1, knockdown of Bad or overexpression of Mcl-1 recapitulated, at least in part, the effect of myr-Akt, suggesting that regulation of Bad and Mcl-1 is involved in PIB5PA-mediated sensitization of melanoma cells to the inhibitors. The role of PIB5PA deficiency in BRAF inhibitor resistance was confirmed by knockdown of PIB5PA, which led to increased growth of BRAF(V600E) melanoma cells selected for resistance to PLX4720. Consistent with its role in vitro, overexpression of

PIB5PA and the MEK inhibitor selumetinib cooperatively inhibited melanoma tumor growth in a xenograft model. Taken together, these results identify loss of PIB5PA as a novel resistance mechanism of melanoma to RAF/MEK inhibitors and suggest that restoration of PIB5PA may be a useful strategy to improve the therapeutic efficacy of the inhibitors in the treatment of melanoma.

[1013]

TÍTULO / TITLE: - The HDAC inhibitor, MPT0E028, enhances erlotinib-induced cell death in EGFR-TKI-resistant NSCLC cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 19;4:e810. doi: 10.1038/cddis.2013.330.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cddis.2013.330](#)

AUTORES / AUTHORS: - Chen MC; Chen CH; Wang JC; Tsai AC; Liou JP; Pan SL; Teng CM

INSTITUCIÓN / INSTITUTION: - Pharmacological Institute, College of Medicine, National Taiwan University, Taipei, Taiwan.

RESUMEN / SUMMARY: - Epidermal growth factor receptor (EGFR), which promotes cell survival and division, is found at abnormally high levels on the surface of many cancer cell types, including many cases of non-small cell lung cancer. Erlotinib (Tarceva), an oral small-molecule tyrosine kinase inhibitor, is a so-called targeted drug that inhibits the tyrosine kinase domain of EGFR, and thus targets cancer cells with some specificity while doing less damage to normal cells. However, erlotinib resistance can occur, reducing the efficacy of this treatment. To develop more effective therapeutic interventions by overcoming this resistance problem, we combined the histone deacetylase inhibitor, MPT0E028, with erlotinib in an effort to increase their antitumor effects in erlotinib-resistant lung adenocarcinoma cells. This combined treatment yielded significant growth inhibition, induced the expression of apoptotic proteins (PARP, gammaH2AX, and caspase-3), increased the levels of acetylated histone H3, and showed synergistic effects in vitro and in vivo. These effects were independent of the mutation status of the genes encoding EGFR or K-Ras. MPT0E028 synergistically blocked key regulators of the EGFR/HER2 signaling pathways, attenuating multiple compensatory pathways (e.g., AKT, extracellular signal-regulated kinase, and c-MET). Our results indicate that this combination therapy might be a promising strategy for facilitating the effects of erlotinib monotherapy by activating various networks. Taken together, our data provide compelling evidence that MPT0E028 has the potential to improve the treatment of heterogeneous and drug-resistant tumors that cannot be controlled with single-target agents.

[1014]

TÍTULO / TITLE: - Interferon-beta Produces Synergistic Combinatory Anti-Tumor Effects with Cisplatin or Pemetrexed on Mesothelioma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 16;8(8):e72709. doi: 10.1371/journal.pone.0072709.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072709](https://doi.org/10.1371/journal.pone.0072709)

AUTORES / AUTHORS: - Li Q; Kawamura K; Yang S; Okamoto S; Kobayashi H; Tada Y; Sekine I; Takiguchi Y; Shingyouji M; Tatsumi K; Shimada H; Hiroshima K; Tagawa M

INSTITUCIÓN / INSTITUTION: - Division of Pathology and Cell Therapy, Chiba Cancer Center Research Institute, Chiba, Japan ; Department of Molecular Biology and Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan.

RESUMEN / SUMMARY: - Interferons (IFNs) have been tested for the therapeutic effects in various types of malignancy, but mechanisms of the anti-tumors effects and the differential biological activities among IFN members are dependent on respective cell types. In this study, we examined growth inhibitory activities of type I and III IFNs on 5 kinds of human mesothelioma cells bearing wild-type p53 gene, and showed that type I IFNs but not type III IFNs decreased the cell viabilities. Moreover, growth inhibitory activities and up-regulated expression levels of the major histocompatibility complexes class I antigens were greater with IFN-beta than with IFN-alpha treatments. Cell cycle analyses demonstrated that type I IFNs increased S- and G2/M-phase populations, and subsequently sub-G1-phase fractions. The cell cycle changes were also greater with IFN-beta than IFN-alpha treatments, and these data collectively showed that IFN-beta had stronger biological activities than IFN-alpha in mesothelioma. Type I IFNs-treated cells increased p53 expression and the phosphorylation levels, and activated apoptotic pathways. A combinatory use of IFN-beta and cisplatin or pemetrexed, both of which are the current first-line chemotherapeutic agents for mesothelioma, produced synergistic anti-tumor effects, which were also evidenced by increased sub-G1-phase fractions. These data demonstrated firstly to our knowledge that IFN-beta produced synergistic anti-tumor effects with cisplatin or pemetrexed on mesothelioma through up-regulated p53 expression.

[1015]

TÍTULO / TITLE: - RuvBL2 Is Involved in Histone Deacetylase Inhibitor PCI-24781-Induced Cell Death in SK-N-DZ Neuroblastoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 16;8(8):e71663. doi: 10.1371/journal.pone.0071663.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071663](https://doi.org/10.1371/journal.pone.0071663)

AUTORES / AUTHORS: - Zhan Q; Tsai S; Lu Y; Wang C; Kwan Y; Ngai S

INSTITUCIÓN / INSTITUTION: - Centre for Soybean Research of Partner State Key Laboratory of Agrobiotechnology and School of Life Sciences, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China.

RESUMEN / SUMMARY: - Neuroblastoma is the second most common solid tumor diagnosed during infancy. The survival rate among children with high-risk

neuroblastoma is less than 40%, highlighting the urgent needs for new treatment strategies. PCI-24781 is a novel hydroxamic acid-based histone deacetylase (HDAC) inhibitor that has high efficacy and safety for cancer treatment. However, the underlying mechanisms of PCI-24781 are not clearly elucidated in neuroblastoma cells. In the present study, we demonstrated that PCI-24781 treatment significantly inhibited tumor growth at very low doses in neuroblastoma cells SK-N-DZ, not in normal cell line HS-68. However, PCI-24781 caused the accumulation of acetylated histone H3 both in SK-N-DZ and HS-68 cell line. Treatment of SK-N-DZ with PCI-24781 also induced cell cycle arrest in G2/M phase and activated apoptosis signaling pathways via the up-regulation of DR4, p21, p53 and caspase 3. Further proteomic analysis revealed differential protein expression profiles between non-treated and PCI-24781 treated SK-N-DZ cells. Totally 42 differentially expressed proteins were identified by MALDI-TOF MS system. Western blotting confirmed the expression level of five candidate proteins including prohibitin, hHR23a, RuvBL2, TRAP1 and PDCD6IP. Selective knockdown of RuvBL2 rescued cells from PCI-24781-induced cell death, implying that RuvBL2 might play an important role in anti-tumor activity of PCI-24781 in SK-N-DZ cells. The present results provide a new insight into the potential mechanism of PCI-24781 in SK-N-DZ cell line.

[1016]

TÍTULO / TITLE: - Enhanced Cytotoxicity from Deoxyguanosine-Enriched T-oligo in Prostate Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nucleic Acid Ther. 2013 Oct;23(5):311-21. doi: 10.1089/nat.2013.0420. Epub 2013 Aug 24.

●● [Enlace al texto completo \(gratis o de pago\) 1089/nat.2013.0420](#)

AUTORES / AUTHORS: - Rankin AM; Forman L; Sarkar S; Faller DV

INSTITUCIÓN / INSTITUTION: - Cancer Center and Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

RESUMEN / SUMMARY: - Prostate cancer represents approximately 10 percent of all cancer cases in men and accounts for more than a quarter of all cancer types. Advances in understanding the molecular mechanisms of prostate cancer progression, however, have not translated well to the clinic. Patients with metastatic and hormone-refractory disease have only palliative options for treatment, as chemotherapy seldom produces durable or complete responses, highlighting the need for novel therapeutic approaches. T-oligo, a single-stranded deoxyribonucleic acid with partial sequence homology to human telomeric DNA, has elicited cytostatic and/or cytotoxic effects in multiple cancer cell types. In contrast, normal primary cells of varying tissue types are resistant to cytotoxic actions of T-oligo, underscoring its potential utility as a novel targeted cancer therapeutic. Mechanistically, T-oligo is hypothesized to interfere with normal telomeric structure and form G-quadruplex structures, thereby inducing

genomic stress in addition to aberrant upregulation of DNA damageresponse pathways. Here, we present data demonstrating the enhanced effectiveness of a deoxyguanosine-enriched sequence of T-oligo, termed (GGTT)₄, which elicits robust cytotoxic effects in prostate cancer cells at lower concentrations than the most recent T-oligo sequence (5'-pGGT TAG GTG TAG GTT T 3') described to date and used for comparison in this study, while exerting no cytotoxic actions on nontransformed human prostate epithelial cells. Additionally, we provide evidence supporting the T-oligo induced activation of cJun N-terminal kinase (JNK) signaling in prostate cancer cells consistent with G-quadruplex formation, thereby significantly advancing the understanding of the T-oligo mechanism of action.

[1017]

TÍTULO / TITLE: - Integrated analysis of drug-induced gene expression profiles predicts novel hERG inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e69513. doi: 10.1371/journal.pone.0069513. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069513](#)

AUTORES / AUTHORS: - Babcock JJ; Du F; Xu K; Wheelan SJ; Li M

INSTITUCIÓN / INSTITUTION: - The Solomon H. Snyder Department of Neuroscience and High Throughput Biology Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America.

RESUMEN / SUMMARY: - Growing evidence suggests that drugs interact with diverse molecular targets mediating both therapeutic and toxic effects. Prediction of these complex interactions from chemical structures alone remains challenging, as compounds with different structures may possess similar toxicity profiles. In contrast, predictions based on systems-level measurements of drug effect may reveal pharmacologic similarities not evident from structure or known therapeutic indications. Here we utilized drug-induced transcriptional responses in the Connectivity Map (CMap) to discover such similarities among diverse antagonists of the human ether-a-go-go related (hERG) potassium channel, a common target of promiscuous inhibition by small molecules. Analysis of transcriptional profiles generated in three independent cell lines revealed clusters enriched for hERG inhibitors annotated using a database of experimental measurements (hERGcentral) and clinical indications. As a validation, we experimentally identified novel hERG inhibitors among the unannotated drugs in these enriched clusters, suggesting transcriptional responses may serve as predictive surrogates of cardiotoxicity complementing existing functional assays.

[1018]

TÍTULO / TITLE: - Saussurea lappa Clarke-Derived Costunolide Prevents TNF alpha - Induced Breast Cancer Cell Migration and Invasion by Inhibiting NF- kappa B Activity.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:936257. doi: 10.1155/2013/936257. Epub 2013 Aug 13.

●● Enlace al texto completo (gratis o de pago) [1155/2013/936257](#)

AUTORES / AUTHORS: - Choi YK; Cho SG; Woo SM; Yun YJ; Jo J; Kim W; Shin YC; Ko SG

INSTITUCIÓN / INSTITUTION: - Laboratory of Clinical Biology and Pharmacogenomics, Center for Clinical Research and Genomics, Department of Preventive Medicine, College of Korean Medicine, Kyung Hee University, 1 Hoegi-dong, Seoul 130-701, Republic of Korea.

RESUMEN / SUMMARY: - Saussurea lappa Clarke (SLC) has been used as a traditional medicine in Korea, China, and Japan for the treatment of abdominal pain and tenesmus. Costunolide, a sesquiterpene lactone isolated from SLC, has diverse medicinal effects. However, the anticancer effects of costunolide are still unclear in breast cancer. In this study, we demonstrate that costunolide suppresses tumor growth and metastases of MDA-MB-231 highly metastatic human breast cancer cells via inhibiting TNFalpha-induced NF-kappaB activation. Costunolide inhibited MDA-MB-231 tumor growth and metastases without affecting body weights in the in vivo mouse orthotopic tumor growth assays. In addition, costunolide inhibited in vitro TNFalpha-induced invasion and migration of MDA-MB-231 cells. Costunolide further suppressed TNFalpha-induced NF-kappaB signaling activation, resulting in a reduced expression of MMP-9, a well-known NF-kappaB-dependent gene to mediate breast cancer cell growth and metastases. Therefore, we conclude that SLC and its derivative costunolide suppress breast cancer growth and metastases by inhibiting TNFalpha-induced NF-kappaB activation, suggesting that costunolide as well as SLC may be promising anticancer drugs, especially for metastatic breast cancer.

[1019]

TÍTULO / TITLE: - Antihistamine use and immunoglobulin E levels in glioma risk and prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Epidemiol. 2013 Aug 29. pii: S1877-7821(13)00119-7. doi: 10.1016/j.canep.2013.08.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.canep.2013.08.004](#)

AUTORES / AUTHORS: - Amirian ES; Marquez-Do D; Bondy ML; Scheurer ME

INSTITUCIÓN / INSTITUTION: - Dan L. Duncan Cancer Center, Baylor College of Medicine, One Baylor Plaza MS:BCM305, Houston, TX 77030, USA; Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza MS:BCM305, Houston, TX 77030, USA. Electronic address: amirian@bcm.edu.

RESUMEN / SUMMARY: - Objective: An inverse association between personal history of allergies/asthma and glioma risk has been fairly consistently reported in the epidemiologic literature. However, the role of regular antihistamine use remains controversial due to a small number of studies reporting contradictory findings. We evaluated the association between regular use of oral antihistamines and glioma risk, adjusting for a number of relevant factors (e.g., immunoglobulin E levels and history of chickenpox). Methods: We used a subset of the Harris County Case-Control Study, which included 362 pathologically confirmed glioma cases and 462 cancer-free controls, to evaluate this association using unconditional multivariable logistic regression. These models were run among the overall study population and stratified by allergy status. Cox regression was utilized to examine whether antihistamine use was associated with mortality among all cases and separately among high-grade cases. Results: Antihistamine use was strongly associated with glioma risk among those with a positive allergy/asthma history (OR: 4.19, 95% CI: 2.06-8.51), but not among those with a negative history (OR: 1.59, 95% CI: 0.95-2.67). There were no significant associations between antihistamine use and survival among cases. Conclusion: The current study implies that regular antihistamine use may increase glioma risk. However, several larger studies are necessary before definitive conclusions can be drawn.

[1020]

TÍTULO / TITLE: - Stapled alpha-helical peptide drug development: A potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Proc Natl Acad Sci U S A. 2013 Sep 3;110(36):E3445-54. doi: 10.1073/pnas.1303002110. Epub 2013 Aug 14.

●● Enlace al texto completo (gratis o de pago) [1073/pnas.1303002110](https://doi.org/10.1073/pnas.1303002110)

AUTORES / AUTHORS: - Chang YS; Graves B; Guerlavais V; Tovar C; Packman K; To KH; Olson KA; Kesavan K; Gangurde P; Mukherjee A; Baker T; Darlak K; Elkin C; Filipovic Z; Qureshi FZ; Cai H; Berry P; Feyfant E; Shi XE; Horstick J; Annis DA; Manning AM; Fotouhi N; Nash H; Vassilev LT; Sawyer TK

INSTITUCIÓN / INSTITUTION: - Aileron Therapeutics, Inc., Cambridge, MA 02139.

RESUMEN / SUMMARY: - Stapled alpha-helical peptides have emerged as a promising new modality for a wide range of therapeutic targets. Here, we report a potent and selective dual inhibitor of MDM2 and MDMX, ATSP-7041, which effectively activates the p53 pathway in tumors in vitro and in vivo. Specifically, ATSP-7041 binds both MDM2 and MDMX with nanomolar affinities, shows submicromolar cellular activities in cancer cell lines in the presence of serum, and demonstrates highly specific, on-target mechanism of action. A high resolution (1.7-Å) X-ray crystal structure reveals its molecular interactions with the target protein MDMX, including multiple contacts with key amino acids as well as a role for the hydrocarbon staple itself in target

engagement. Most importantly, ATSP-7041 demonstrates robust p53-dependent tumor growth suppression in MDM2/MDMX-overexpressing xenograft cancer models, with a high correlation to on-target pharmacodynamic activity, and possesses favorable pharmacokinetic and tissue distribution properties. Overall, ATSP-7041 demonstrates in vitro and in vivo proof-of-concept that stapled peptides can be developed as therapeutically relevant inhibitors of protein-protein interaction and may offer a viable modality for cancer therapy.

[1021]

TÍTULO / TITLE: - Update on hepatocellular carcinoma breakthroughs: Poly(ADP-ribose) polymerase inhibitors as a promising therapeutic strategy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Res Hepatol Gastroenterol. 2013 Aug 13. pii: S2210-7401(13)00149-6. doi: 10.1016/j.clinre.2013.07.006.

●● Enlace al texto completo (gratis o de pago) 1016/j.clinre.2013.07.006

AUTORES / AUTHORS: - Guillot C; Hall J; Herceg Z; Merle P; Chemin I

INSTITUCIÓN / INSTITUTION: - UMR INSERM U1052 CNRS5286, CRCL, 151, cours Albert-Thomas, 69008 Lyon, France; Universite Lyon-1, 69622 Villeurbanne, France; International Agency for Research on Cancer, 150, cours Albert-Thomas, 69424 Lyon cedex 03, France.

RESUMEN / SUMMARY: - Hepatocellular carcinoma is the most common form of primary liver cancer which is the fifth most common cancer in men and the seventh in women and the third most common cause of cancer-related death worldwide. Only 10-20% of patients are eligible for curative treatments that result in a 5-year survival rate of 40% to 70%. Therefore, the development of novel treatment options is necessary for the majority of patients and remains a considerable challenge. Conformal radiotherapy is used in certain circumstances and preliminary data obtained from phase ½ trials are showing promising curative effects. There is thus an interest in identifying drugs that can be exploited to enhance radiation sensitivity that could be used in therapy and might improve clinical outcome. Small molecules inhibitors of poly(ADP-ribose) polymerases (PARP) are an example of a radio- and chemo-sensitizing drug, as well as being an efficient single agent treatment in certain genetic backgrounds. In this review, we discuss the role of PARP-1 in hepatocellular carcinoma and present the results of preclinical studies that have assessed the potential of PARP inhibition as a single treatment or combined with chemotherapy or radiotherapy for the treatment of hepatocellular carcinoma.

[1022]

TÍTULO / TITLE: - Citrate induces apoptosis of the acute monocytic leukemia U937 cell line through regulation of HIF1alpha signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Nov;8(5):1379-1384. doi: 10.3892/mmr.2013.1702. Epub 2013 Sep 24.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1702](https://doi.org/10.3892/mmr.2013.1702)

AUTORES / AUTHORS: - Xu X; Li B; Huang P; Wan X; Qin Y; Zhou L; Liu H; Bai H; Gao Y; Wang C; Meng X

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai 200080, P.R. China.

RESUMEN / SUMMARY: - The present study aimed to investigate the antitumor effect of citrate on acute monocytic leukemia (AML) and its mechanisms. The apoptosis of the AML cell line, U937, was assessed by MTT and Hoechst staining, the expression of Bcl2, caspases3 and 9, hypoxia-inducible factor 1alpha (HIF1alpha) and its target gene GLUT1, were assayed by western blotting and the role of HIF1alpha was evaluated through siRNA. The results showed that citrate inhibits the expression of Bcl2, while it induces the activation of caspases3 and 9. In addition, citrate induces U937 apoptosis in a dose and time-dependent manner by regulating the expression of HIF1alpha and its downstream target GLUT1. The results suggest that citrate performs an anti-acute monocytic leukemia action by targeting HIF1alpha signaling and may be a promising clinical approach.

[1023]

TÍTULO / TITLE: - Overexpression of epidermal growth factor receptor as a prognostic factor in colorectal cancer on the basis of the Allred scoring system.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jul 24;6:967-76. doi: 10.2147/OTT.S42446. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S42446](https://doi.org/10.2147/OTT.S42446)

AUTORES / AUTHORS: - Rokita M; Stec R; Bodnar L; Charkiewicz R; Korniluk J; Smoter M; Cichowicz M; Chyczewski L; Niklinski J; Kozłowski W; Szczylik C

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Military Institute of Medicine, Central Teaching Hospital, Warsaw Poland.

RESUMEN / SUMMARY: - BACKGROUND: Overexpression of epidermal growth factor receptor (EGFR) is found in many types of neoplasms. The aim of the study was to evaluate EGFR expression in colorectal cancer (CRC) specimens and to determine whether EGFR expression correlates with clinicopathological data and overall survival. PATIENTS AND METHODS: Tissue specimens from 181 consecutive CRC patients treated at the Military Institute of Medicine in 2006-2010 were collected and examined for EGFR expression, by immunohistochemistry staining. The staining intensity and percentage of cells with membranous EGFR expression were scored and then grouped according to the parameters of the Allred Scoring system. Cutoff values were subjected to further statistical analysis. Univariate tests and a multivariate Cox proportional hazards model were used in data analysis. RESULTS: EGFR was

overexpressed in 96 of 181 CRC specimens (53%). EGFR expression was not correlated with other clinicopathological variables. On univariate analysis, overexpression of EGFR, determined by PS (percentage score) (>3) and total score (sum of PS and intensity score) (>4), was associated with poor overall survival. On multivariate analysis, EGFR overexpression (PS > 3) was an independent adverse prognostic factor (hazard ratio [HR] 1.62; 95% confidence interval [CI]: 1.03-2.53). Elevated carcinoembryonic antigen (CEA) serum concentration before treatment, performance status (World Health Organization [WHO]-2), and tumor localized in colon and liver metastases were also independent unfavorable prognostic factors. CONCLUSION: EGFR overexpression (PS > 3) in a CRC patient population was an independent adverse prognostic factor. Implementation of the Allred Scoring system criteria into clinical practice might facilitate treatment decisions in CRC patients.

[1024]

TÍTULO / TITLE: - Resveratrol-Loaded Nanoparticles Based on Poly(epsilon-caprolactone) and Poly(d,l-lactic-co-glycolic acid)-Poly(ethylene glycol) Blend for Prostate Cancer Treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Pharm. 2013 Sep 4.

●● [Enlace al texto completo \(gratis o de pago\) 1021/mp400342f](#)

AUTORES / AUTHORS: - Sanna V; Siddiqui IA; Sechi M; Mukhtar H

INSTITUCIÓN / INSTITUTION: - Department of Chemistry and Pharmacy, Laboratory of Nanomedicine, University of Sassari, 07100 Sassari, Italy.

RESUMEN / SUMMARY: - Nanoencapsulation of antiproliferative and chemopreventive phytoalexin trans-resveratrol (RSV) is likely to provide protection against degradation, enhancement of bioavailability, improvement in intracellular penetration and control delivery. In this study, polymeric nanoparticles (NPs) encapsulating RSV (nano-RSV) as novel prototypes for prostate cancer (PCa) treatment were designed, characterized and evaluated using human PCa cells. Nanosystems, composed of a biocompatible blend of poly(epsilon-caprolactone) (PCL) and poly(d,l-lactic-co-glycolic acid)-poly(ethylene glycol) conjugate (PLGA-PEG-COOH), were prepared by a nanoprecipitation method, and characterized in terms of morphology, particle size and zeta potential, encapsulation efficiency, thermal analyses, and in vitro release studies. Cellular uptake of NPs was then evaluated in PCa cell lines DU-145, PC-3, and LNCaP using confocal fluorescence microscopy, and antiproliferative efficacy was assessed using MTT assay. With encapsulation efficiencies ranging from 74% to 98%, RSV was successfully loaded in PCL:PLGA-PEG-COOH NPs, which showed an average diameter of 150 nm. NPs were able to control the RSV release at pH 6.5 and 7.4, mimicking the acidic tumoral microenvironment and physiological conditions, respectively, with only 55% of RSV released within 7 h. In gastrointestinal simulated fluids, NPs released about 55% of RSV in the first 2 h in acidic medium, and their total RSV content within the

subsequent 5 h at pH 7.4. Confocal fluorescence microscopy observations revealed that NPs were efficiently taken up by PCa cell lines. Furthermore, nano-RSV significantly improved the cytotoxicity compared to that of free RSV toward all three cell lines, at all tested concentrations (from 10 μ M to 40 μ M), proving a consistent sensitivity toward both the androgen-independent DU-145 and hormone-sensitive LNCaP cells. Our findings support the potential use of developed nanoprototypes for the controlled delivery of bioactive RSV for PCa chemoprevention/chemotherapy.

[1025]

TÍTULO / TITLE: - Predictive modeling of in vivo response to gemcitabine in pancreatic cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS Comput Biol. 2013 Sep;9(9):e1003231. doi: 10.1371/journal.pcbi.1003231. Epub 2013 Sep 19.

●● [Enlace al texto completo \(gratis o de pago\) 1371/journal.pcbi.1003231](#)

AUTORES / AUTHORS: - Lee JJ; Huang J; England CG; McNally LR; Frieboes HB

INSTITUCIÓN / INSTITUTION: - School of Medicine, University of Louisville, Louisville, Kentucky, United States of America.

RESUMEN / SUMMARY: - A clear contradiction exists between cytotoxic in-vitro studies demonstrating effectiveness of Gemcitabine to curtail pancreatic cancer and in-vivo studies failing to show Gemcitabine as an effective treatment. The outcome of chemotherapy in metastatic stages, where surgery is no longer viable, shows a 5-year survival <5%. It is apparent that in-vitro experiments, no matter how well designed, may fail to adequately represent the complex in-vivo microenvironmental and phenotypic characteristics of the cancer, including cell proliferation and apoptosis. We evaluate in-vitro cytotoxic data as an indicator of in-vivo treatment success using a mathematical model of tumor growth based on a dimensionless formulation describing tumor biology. Inputs to the model are obtained under optimal drug exposure conditions in-vitro. The model incorporates heterogeneous cell proliferation and death caused by spatial diffusion gradients of oxygen/nutrients due to inefficient vascularization and abundant stroma, and thus is able to simulate the effect of the microenvironment as a barrier to effective nutrient and drug delivery. Analysis of the mathematical model indicates the pancreatic tumors to be mostly resistant to Gemcitabine treatment in-vivo. The model results are confirmed with experiments in live mice, which indicate uninhibited tumor proliferation and metastasis with Gemcitabine treatment. By extracting mathematical model parameter values for proliferation and death from monolayer in-vitro cytotoxicity experiments with pancreatic cancer cells, and simulating the effects of spatial diffusion, we use the model to predict the drug response in-vivo, beyond what would have been expected from sole consideration of the cancer intrinsic resistance. We conclude that this integrated experimental/computational approach may enhance understanding of

pancreatic cancer behavior and its response to various chemotherapies, and, further, that such an approach could predict resistance based on pharmacokinetic measurements with the goal to maximize effective treatment strategies.

[1026]

TÍTULO / TITLE: - A Polymorphism at the 3'-UTR Region of the Aromatase Gene Is Associated with the Efficacy of the Aromatase Inhibitor, Anastrozole, in Metastatic Breast Carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Sep 13;14(9):18973-88. doi: 10.3390/ijms140918973.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140918973](#)

AUTORES / AUTHORS: - Liu L; Bai YX; Zhou JH; Sun XW; Sui H; Zhang WJ; Yuan HH; Xie R; Wei XL; Zhang TT; Huang P; Li YJ; Wang JX; Zhao S; Zhang QY

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, The Affiliated Tumor Hospital, Harbin Medical University, Haping Road 150 of Nangang District, Harbin 150081, Heilongjiang, China. zhma19650210@yeah.net.

RESUMEN / SUMMARY: - Estrogen-related genes and the fat mass and obesity-associated (FTO) gene play a critical role in estrogen metabolism, and those polymorphisms are associated with a poor prognosis in breast cancer. However, little is known about the association between these polymorphisms and the efficacy of anastrozole. The aim was to investigate the impact of the genetic polymorphisms, CYP19A1, 17-beta-HSD-1 and FTO, on the response to anastrozole in metastatic breast carcinoma (MBC) and to evaluate the impact of those polymorphisms on various clinicopathologic features. Two-hundred seventy-two women with hormone receptor-positive MBC treated with anastrozole were identified retrospectively. DNA was extracted from peripheral blood and genotyped for five variants in three candidate genes. Time to progression was improved in patients carrying the variant alleles of rs4646 when compared to patients with the wild-type allele (16.40 months versus 13.52 months; $p = 0.049$). The rs4646 variant alleles were significantly associated with longer overall survival (37.3 months versus 31.6 months; $p = 0.007$). This relationship was not observed with the rs10046, rs2830, rs9926298 and rs9939609 polymorphisms. The findings of this study indicate that rs4646 polymorphism in the CYP19A1 gene may serve as a prognostic maker of the response to anastrozole in patients with MBC who are treated with anastrozole.

[1027]

TÍTULO / TITLE: - A Chimeric SERM-Histone Deacetylase Inhibitor Approach to Breast Cancer Therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ChemMedChem. 2013 Aug 16. doi: 10.1002/cmdc.201300270.

●● Enlace al texto completo (gratis o de pago) [1002/cmdc.201300270](#)

AUTORES / AUTHORS: - Patel HK; Siklos MI; Abdelkarim H; Mendonca EL; Vaidya A; Petukhov PA; Thatcher GR

INSTITUCIÓN / INSTITUTION: - Department of Medicinal Chemistry and Pharmacognosy, University of Illinois College of Pharmacy, UIC, 833 S. Wood St., Chicago, IL 60612-7231 (USA).

RESUMEN / SUMMARY: - Breast cancer remains a significant cause of death in women, and few therapeutic options exist for estrogen receptor negative (ER (-)) cancers. Epigenetic reactivation of target genes using histone deacetylase (HDAC) inhibitors has been proposed in ER (-) cancers to resensitize to therapy using selective estrogen receptor modulators (SERMs) that are effective in ER (+) cancer treatment. Based upon preliminary studies in ER (+) and ER (-) breast cancer cells treated with combinations of HDAC inhibitors and SERMs, hybrid drugs, termed SERMostats, were designed with computational guidance. Assay for inhibition of four type I HDAC isoforms and antagonism of estrogenic activity in two cell lines yielded a SERMostat with 1-3 µM potency across all targets. The superior hybrid caused significant cell death in ER (-) human breast cancer cells and elicited cell death at the same concentration as the parent SERM in combination treatment and at an earlier time point.

[1028]

TÍTULO / TITLE: - Epigenetic therapy of non-small cell lung cancer using decitabine (5-aza-2'-deoxycytidine).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Oncol. 2013;3:188. doi: 10.3389/fonc.2013.00188.

●● [Enlace al texto completo \(gratis o de pago\) 3389/fonc.2013.00188](#)

AUTORES / AUTHORS: - Mompalmer RL

INSTITUCIÓN / INSTITUTION: - Departement de Pharmacologie, Centre de Recherche du CHU Sainte-Justine, Université de Montreal, Montreal, QC, Canada.

RESUMEN / SUMMARY: - Epigenetic analysis shows that many genes that suppress malignancy are silenced by aberrant DNA methylation in lung cancer. Many of these genes are interesting targets for reactivation by the inhibitor of DNA methylation, decitabine (5-aza-2'-deoxycytidine, DAC). A pilot study on intense dose DAC showed promising results in patients with metastatic non-small cell lung cancer (NSCLC). However, subsequent clinical studies using low dose DAC were not very effective against NSCLC and interest in this therapy diminished. Recently, interesting responses were observed in a patient with NSCLC following treatment with a combination of the related inhibitor of DNA methylation, 5-azacytidine, and an inhibitor of histone deacetylation. This finding has generated a renewed interest in the epigenetic therapy of lung cancer. Preclinical studies indicate that DAC has remarkable chemotherapeutic potential for tumor therapy. This epigenetic agent has a delayed and prolonged epigenetic action on tumor cells. This delayed action should be taken into

consideration in the design and evaluation of clinical studies on DAC. Future research should be directed at finding the optimal dose-schedule of de DAC for the treatment of NSCLC.

[1029]

TÍTULO / TITLE: - Overexpression of high mobility group A1 protein in human uveal melanomas: implication for prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e68724. doi: 10.1371/journal.pone.0068724. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0068724

AUTORES / AUTHORS: - Qu Y; Wang Y; Ma J; Zhang Y; Meng N; Li H; Wang Y; Wei W

INSTITUCIÓN / INSTITUTION: - Department of Ophthalmology, Qilu Hospital of Shandong University, Jinan, China. drquyi@gmail.com

RESUMEN / SUMMARY: - There is increasing evidence that the high mobility group A1 (HMGA1) protein, which functions as a transcriptional master regulator, plays critical roles in tumor progression. We evaluated HMGA1 expression in 89 primary uveal melanomas (UM) by immunohistochemistry to determine the clinicopathological and prognostic value of HMGA1 in UM after adjusting for other prognostic variables. Nuclear expression of HMGA1 was detected in 44% UMs. High expression levels of HMGA1 were more frequent in UMs with high levels of epithelioid cell pattern, mitoses count, and Ki67 labeling index ($P = 0.025$, $P < 0.0001$, $P = 0.0018$; respectively), and HMGA1 expression levels were directly correlated with Ki67 labeling indexes and mitoses counts ($R = 0.31$, $P < 0.0001$; $R = 0.27$, $P < 0.0068$; respectively). High expression of HMGA1 was also independently associated with an increased risk of distant metastases as determined using the Cox proportional hazards regression model (multivariate hazard ratio: 3.44; 95% confidence interval: 1.56-7.60; log rank $P = 0.0022$). Moreover, high HMGA1 expression was associated with shorter UM-specific survival (multivariate hazard ratio: 2.41; 95% confidence interval: 1.10-5.53; log rank $P = 0.041$). These findings suggest that high levels of HMGA1 are associated with adverse clinical outcomes in UM patients and that further evaluation of HMGA1 as a potential therapeutic target in UM is warranted.

[1030]

TÍTULO / TITLE: - Evaluating use characteristics for the oncoType dx 21-gene recurrence score and concordance with chemotherapy use in early-stage breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Oncol Pract. 2013 Jul 1;9(4):182-7. doi: 10.1200/JOP.2012.000638. Epub 2013 Feb 12.

●● Enlace al texto completo (gratis o de pago) 1200/JOP.2012.000638

AUTORES / AUTHORS: - Chen C; Dhanda R; Tseng WY; Forsyth M; Patt DA

INSTITUCIÓN / INSTITUTION: - McKesson Specialty Health, The Woodlands; Texas Oncology, Austin, TX; and Rocky Mountain Cancer Center, Greenwood Village, CO.

RESUMEN / SUMMARY: - PURPOSE: Oncotype Dx 21-gene assay recurrence score (RS) predicts recurrence of early-stage breast cancer (ESBC). We investigated whether patient, tumor, or practice characteristics drive its use and explored Oncotype DX RS and chemotherapy use in subgroups. METHODS: Patients with ESBC with documented estrogen receptor-positive, lymph node-negative, human epidermal growth factor receptor 2-negative tumors registered within McKesson Specialty Health's iKnowMed electronic health record were included. Patient and practice characteristics by region and size were analyzed. The association between Oncotype DX RS value and use of chemotherapy were assessed. RESULTS: The study included 6,229 patients. Of these, 1,822 (29%) had an Oncotype DX RS result. Test use was 36%, 38%, 34%, 25%, and 6%, respectively, in patients age \leq 45, 46-55, 56-65, 66-75, and \geq 76 years; 33%, 25%, and 9% in patients with Eastern Cooperative Oncology Group performance status of 0, 1, and \geq 2; 7%, 9%, 25%, 38%, 27%, and 10% in T1mic, T1a, T1b, T1c, T2, and T3 tumors; and 26%, 32%, and 33% for grades 1, 2, and 3 tumors. Of the 1,822 patients with available Oncotype DX RS, adjuvant chemotherapy use was 6%, 42%, and 84% in the low-, intermediate-, and high-risk groups. CONCLUSION: Patients who were younger, had better ECOG performance status, or had higher grade tumors were more likely to undergo RS testing. It appears that the RS test may have influenced the decision about whether to administer adjuvant chemotherapy: a low RS score was associated with lower chemotherapy use and a high RS score was associated with higher chemotherapy use.

[1031]

TÍTULO / TITLE: - Antibody-based delivery of interleukin-2 to neovasculature has potent activity against acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Sci Transl Med. 2013 Sep 4;5(201):201ra118. doi: 10.1126/scitranslmed.3006221.

●● Enlace al texto completo (gratis o de pago) [1126/scitranslmed.3006221](https://doi.org/10.1126/scitranslmed.3006221)

AUTORES / AUTHORS: - Gutbrodt KL; Schliemann C; Giovannoni L; Frey K; Pabst T; Klapper W; Berdel WE; Neri D

INSTITUCIÓN / INSTITUTION: - Department of Chemistry and Applied Biosciences, ETH Zurich, Wolfgang-Pauli-Strasse 10, CH-8093 Zurich, Switzerland.

RESUMEN / SUMMARY: - Acute myeloid leukemia (AML) is a rapidly progressing disease that is accompanied by a strong increase in microvessel density in the bone marrow. This observation prompted us to stain biopsies of AML and acute lymphoid leukemia (ALL) patients with the clinical-stage human monoclonal antibodies F8, L19, and F16 directed against markers of tumor angiogenesis. The analysis revealed that the F8 and F16 antibodies strongly stained 70% of AML and 75% of ALL bone marrow specimens,

whereas chloroma biopsies were stained with all three antibodies. Therapy experiments performed in immunocompromised mice bearing human NB4 leukemia with the immunocytokine F8-IL2 [consisting of the F8 antibody fused to human interleukin-2 (IL-2)] mediated a strong inhibition of AML progression. This effect was potentiated by the addition of cytarabine, promoting complete responses in 40% of treated animals. Experiments performed in immunocompetent mice bearing C1498 murine leukemia revealed long-lasting complete tumor eradication in all treated mice. The therapeutic effect of F8-IL2 was mediated by both natural killer cells and CD8(+) T cells, whereas CD4(+) T cells appeared to be dispensable, as determined in immunodepletion experiments. The treatment of an AML patient with disseminated extramedullary AML manifestations with F16-IL2 (consisting of the F16 antibody fused to human IL-2, currently being tested in phase 2 clinical trials in patients with solid tumors) and low-dose cytarabine showed significant reduction of AML lesions and underlines the translational potential of vascular tumor-targeting antibody-cytokine fusions for the treatment of patients with leukemia.

[1032]

TÍTULO / TITLE: - Do hENT1 and RRM1 predict the clinical benefit of gemcitabine in pancreatic cancer?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomark Med. 2013 Aug;7(4):663-71. doi: 10.2217/bmm.13.48.

●● [Enlace al texto completo \(gratis o de pago\) 2217/bmm.13.48](#)

AUTORES / AUTHORS: - Jordheim LP; Dumontet C

INSTITUCIÓN / INSTITUTION: - University of Lyon, F-69000 Lyon, France. lars-petter.jordheim@univ-lyon1.fr

RESUMEN / SUMMARY: - Gemcitabine is a nucleoside analog that is indicated in the treatment of pancreatic cancer. In order to provide a better use of this drug, the search for immunohistological markers is a hot topic in the field of pancreatic cancer. In particular, the use of nucleoside transporter hENT1 and the intracellular target of gemcitabine RRM1 are current subjects for discussion. We have analyzed the majority of studies of hENT1 and RRM1 on pancreatic cancer, and will discuss the further directions that might be followed in order to integrate these proteins in routine clinical practice. The data that is currently available would benefit from the completion of well-designed randomized trials in order to confirm the clinical value of hENT1 and RRM1 as biomarkers in pancreatic cancer patients.

[1033]

TÍTULO / TITLE: - Green Tea Catechins: Proposed Mechanisms of Action in Breast Cancer Focusing on The Interplay Between Survival and Apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Anticancer Agents Med Chem. 2013 Sep 26.

AUTORES / AUTHORS: - Yiannakopoulou EC

INSTITUCIÓN / INSTITUTION: - Department of Basic Medical Lessons, Faculty of Health and Caring Professions Technological Educational Institute of Athens, Eleutheriou Benizelou 106 Kallithea 17676, Athens, Greece. nyiannak@teiath.gr.

RESUMEN / SUMMARY: - Recent data have shown strong chemopreventive and possibly cancer chemotherapeutic effects of green tea polyphenols against cancer. Despite advances in breast cancer treatment, mortality from breast cancer is still high. Undoubtedly novel treatment strategies are needed for chemoprevention of high risk women and for the treatment of receptor negative breast cancer. Green tea catechins have been shown to inhibit proliferation of breast cancer cells and to block carcinogenesis. This review attempts a critical presentation of the mechanisms of action of green tea catechins in breast cancer. Several mechanisms of action of green tea catechins in breast cancer have been proposed including modulation of extracellular signalling, induction of apoptosis through redox regulation, or through modulation of epigenetic alterations. A number of molecular targets of green tea catechins have been suggested i.e molecular chaperones, telomerase, apoptotic cascade. Although the molecular links among the proposed mechanisms of action of green tea catechins are often missing, it must be emphasized that all the proposed mechanisms indicate that green tea catechins inhibit growth and /or promote apoptosis. It would be interesting if future experimental trials could take into account that green tea catechins are multi-target agents and attempt to link every novel proposed target with the other already proposed targets of green tea catechins.

[1034]

TÍTULO / TITLE: - Epigonal Conditioned Media from Bonnethead Shark, *Sphyrna tiburo*, Induces Apoptosis in a T-Cell Leukemia Cell Line, Jurkat E6-1.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mar Drugs. 2013 Aug 26;11(9):3224-57. doi: 10.3390/md11093224.

●● Enlace al texto completo (gratuito o de pago) [3390/md11093224](#)

AUTORES / AUTHORS: - Walsh CJ; Luer CA; Yordy JE; Cantu T; Miedema J; Leggett SR; Leigh B; Adams P; Ciesla M; Bennett C; Bodine AB

INSTITUCIÓN / INSTITUTION: - Marine Immunology Program, Mote Marine Laboratory, 1600 Ken Thompson Parkway, Sarasota, FL 34236, USA. cjwalsh@mote.org.

RESUMEN / SUMMARY: - Representatives of Subclass Elasmobranchii are cartilaginous fish whose members include sharks, skates, and rays. Because of their unique phylogenetic position of being the most primitive group of vertebrates to possess all the components necessary for an adaptive immune system, the immune regulatory compounds they possess may represent the earliest evolutionary forms of novel compounds with the potential for innovative therapeutic applications. Conditioned medium, generated from short term culture of cells from the epigonal organ of

bonnethead sharks (*Sphyrna tiburo*), has been shown to have potent reproducible cytotoxic activity against a variety of human tumor cell lines in vitro. Existing data suggest that epigonal conditioned medium (ECM) exerts this cytotoxic activity through induction of apoptosis in target cells. This manuscript describes apoptosis induction in a representative tumor cell line, Jurkat E6-1, in response to treatment with ECM at concentrations of 1 and 2 mg/mL. Data indicate that ECM exposure initiates the mitochondrial pathway of apoptosis through activation of caspase enzymes. Future purification of ECM components may result in the isolation of an immune-regulatory compound with potential therapeutic benefit for treatment of human cancer.

[1035]

TÍTULO / TITLE: - PKR negatively regulates leukemia progression in association with PP2A activation, Bcl-2 inhibition and increased apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Blood Cancer J. 2013 Sep 6;3:e144. doi: 10.1038/bcj.2013.42.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bcj.2013.42](#)

AUTORES / AUTHORS: - Cheng X; Bennett RL; Liu X; Byrne M; Stratford May W

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Hematology and Oncology and the University of Florida Shands Cancer Center, University of Florida, Gainesville, FL, USA.

RESUMEN / SUMMARY: - Reduced expression and activity of the proapoptotic, double-stranded RNA-dependent protein kinase, PKR (protein kinase R) is observed in breast, lung and various leukemias, suggesting that loss of PKR potentiates transformation. Now we report that decreased PKR activity inhibits chemotherapy-induced apoptosis of leukemia cells both in vitro and in vivo. Inhibition of PKR expression or activity reduces protein phosphatase 2^a (PP2A) activity, a B-cell lymphoma 2 (Bcl-2) phosphatase, resulting in enhanced Bcl-2 phosphorylation. Thus, inhibition of PKR activity leads to hyperphosphorylation of Bcl-2, stabilization of Bcl-2/Bax interaction and decreased Bax insertion into the outer mitochondrial membrane. Treatment with the PP2A activator, FTY720, restores Bcl-2 dephosphorylation and apoptosis in cells with reduced PKR expression following stress. Significantly, xenografts of REH leukemic cells with reduced PKR display significantly increased tumor volume, increased resistance to doxorubicin treatment and shorter survival. Importantly, FTY720 treatment restores sensitivity to chemotherapy and prolongs overall survival of these mice. Collectively, these findings suggest that PP2A activation is a downstream target of PKR and the PKR/PP2A signaling axis is required for rapid and potent stress-induced apoptosis. Importantly, loss of PKR promotes leukemia progression and may serve as a biomarker for predicting chemosensitivity.

[1036]

TÍTULO / TITLE: - Bone marrow recovery and subsequent chemotherapy following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody j591 in men with metastatic castration-resistant prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Oncol. 2013 Aug 26;3:214. doi: 10.3389/fonc.2013.00214.

●● Enlace al texto completo (gratis o de pago) [3389/fonc.2013.00214](#)

AUTORES / AUTHORS: - Tagawa ST; Akhtar NH; Nikolopoulou A; Kaur G; Robinson B; Kahn R; Vallabhajosula S; Goldsmith SJ; Nanus DM; Bander NH

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Hematology and Medical Oncology, Weill Cornell Medical College , New York, NY , USA ; Department of Urology, Weill Cornell Medical College , New York, NY , USA.

RESUMEN / SUMMARY: - Radioimmunotherapy (RIT) has demonstrated efficacy with acceptable toxicity leading to approval in non-Hodgkin's lymphoma, but has been slower to develop for the treatment of advanced solid tumors. Prostate cancer (PC) represents a good candidate for RIT based upon high exposure to circulating antibodies at common disease sites with a specific, highly expressed cell-surface antigen of prostate-specific membrane antigen. Four phase I and II trials utilizing (177)Lu- or (90)Y-J591 have been reported. Long-term toxicity and chemotherapy administration was analyzed. As expected, the only serious toxicity observed was myelosuppression. Grade 4 thrombocytopenia occurred in 33.3% without significant hemorrhage and grade 4 neutropenia occurred in 17.3% with 0.07% febrile neutropenia. Nearly all subjects (97.3%) recovered to grade 0 or 1 platelets and all had complete neutrophil recovery. The majority (81.3%) received chemotherapy at any time, with 61.3% receiving chemotherapy following RIT. Ten subjects underwent bone marrow biopsies at some point in their disease course following RIT for low counts; all had diffuse PC infiltration without evidence of myelodysplasia or leukemia. As expected, myelosuppression occurs following therapeutic doses of RIT for men with metastatic castration-resistant PC. However, toxicity is predictable and self-limited, with the majority of patients who do not refuse able to receive cytotoxic chemotherapy following RIT.

[1037]

TÍTULO / TITLE: - Prognostic values of osteopontin-c, E-cadherin and beta-catenin in breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Epidemiol. 2013 Sep 5. pii: S1877-7821(13)00120-3. doi: 10.1016/j.canep.2013.08.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.canep.2013.08.005](#)

AUTORES / AUTHORS: - Pang H; Lu H; Song H; Meng Q; Zhao Y; Liu N; Lan F; Liu Y; Yan S; Dong X; Cai L

INSTITUCIÓN / INSTITUTION: - Department of Internal Medical Oncology, the Affiliated Tumor Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To determine the correlation of cell adhesion molecules (osteopontin-c, E-cadherin and beta-catenin) with clinicopathological characteristics in breast cancer. **METHODS:** Immunostaining of osteopontin-c, E-cadherin and beta-catenin were conducted in 170 samples of breast cancer and 30 samples of adjacent normal breast tissues. The correlation of osteopontin-c, E-cadherin and beta-catenin expression level with clinicopathological characteristics was evaluated by Pearson's chi-square and Wilcoxon rank-sum test. Univariate and multivariate Cox hazard regression model was used to assess the prognostic values of osteopontin-c, E-cadherin and beta-catenin in clinical outcome of breast cancer. **RESULTS:** A higher level of osteopontin-c whereas lower levels of E-cadherin and beta-catenin were observed in breast cancer as compared with the normal breast tissues. The expression of osteopontin-c was negatively associated with the expression of E-cadherin and beta-catenin. The expression of osteopontin-c correlated with lymph node metastasis, and advanced TNM stage and histologic grade. The expression of E-cadherin correlated with low histologic grade; and beta-catenin with low TNM stage and histological grade. Moreover, high osteopontin-c level correlated with tumor recurrence or metastasis as well as triple negative subtype. The expression of osteopontin-c was an independent prognostic factor for both disease-free and overall survival of breast cancer patients. **CONCLUSION:** The data suggest that the expression of osteopontin-c could serve as a prognostic factor of breast cancer.

[1038]

TÍTULO / TITLE: - Retinoblastoma protein regulates the crosstalk between autophagy and apoptosis, and favors glioblastoma resistance to etoposide.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 15;4:e767. doi: 10.1038/cddis.2013.283.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.283](#)

AUTORES / AUTHORS: - Biasoli D; Kahn SA; Cornelio TA; Furtado M; Campanati L; Chneiweiss H; Moura-Neto V; Borges HL

INSTITUCIÓN / INSTITUTION: - Instituto de Ciencias Biomedicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

RESUMEN / SUMMARY: - Glioblastomas (GBMs) are devastating tumors of the central nervous system, with a poor prognosis of 1-year survival. This results from a high resistance of GBM tumor cells to current therapeutic options, including etoposide (VP-16). Understanding resistance mechanisms may thus open new therapeutic avenues. VP-16 is a topoisomerase inhibitor that causes replication fork stalling and, ultimately, the formation of DNA double-strand breaks and apoptotic cell death. Autophagy has been identified as a VP-16 treatment resistance mechanism in tumor cells. Retinoblastoma protein (RB) is a classical tumor suppressor owing to its role in G1/S

cell cycle checkpoint, but recent data have shown RB participation in many other cellular functions, including, counterintuitively, negative regulation of apoptosis. As GBMs usually display an amplification of the EGFR signaling involving the RB protein pathway, we questioned whether RB might be involved in mechanisms of resistance of GBM cells to VP-16. We observed that RB silencing increased VP-16-induced DNA double-strand breaks and p53 activation. Moreover, RB knockdown increased VP-16-induced apoptosis in GBM cell lines and cancer stem cells, the latter being now recognized essential to resistance to treatments and recurrence. We also showed that VP-16 treatment induced autophagy, and that RB silencing impaired this process by inhibiting the fusion of autophagosomes with lysosomes. Taken together, our data suggest that RB silencing causes a blockage on the VP-16-induced autophagic flux, which is followed by apoptosis in GBM cell lines and in cancer stem cells. Therefore, we show here, for the first time, that RB represents a molecular link between autophagy and apoptosis, and a resistance marker in GBM, a discovery with potential importance for anticancer treatment.

[1039]

TÍTULO / TITLE: - Knockdown a water channel protein, aquaporin-4, induced glioblastoma cell apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e66751. doi: 10.1371/journal.pone.0066751.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0066751](#)

AUTORES / AUTHORS: - Ding T; Zhou Y; Sun K; Jiang W; Li W; Liu X; Tian C; Li Z; Ying G; Fu L; Gu F; Li W; Ma Y

INSTITUCIÓN / INSTITUTION: - Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Breast Cancer Prevention and Therapy of the Ministry of Education; Key Laboratory of Cancer Prevention and Therapy of Tianjin, Tianjin, China.

RESUMEN / SUMMARY: - Glioblastomas are the most aggressive forms of primary brain tumors due to their tendency to invade surrounding healthy brain tissues, rendering them largely incurable. The water channel protein, Aquaporin-4 (AQP4) is a key molecule for maintaining water and ion homeostasis in the central nervous system and has recently been reported with cell survival except for its well-known function in brain edema. An increased AQP4 expression has been demonstrated in glioblastoma multiforme (GBM), suggesting it is also involved in malignant brain tumors. In this study, we show that siRNA-mediated down regulation of AQP4 induced glioblastoma cell apoptosis in vitro and in vivo. We further show that several apoptotic key proteins, Cytochrome C, Bcl-2 and Bad are involved in AQP4 signaling pathways. Our results indicate that AQP4 may serve as an anti-apoptosis target for therapy of glioblastoma.

[1040]

TÍTULO / TITLE: - DNA methylation biomarkers as diagnostic and prognostic tools in colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Med (Berl). 2013 Sep 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00109-013-1088-z](#)

AUTORES / AUTHORS: - Gyparaki MT; Basdra EK; Papavassiliou AG

INSTITUCIÓN / INSTITUTION: - Department of Biological Chemistry, University of Athens Medical School, 11527, Athens, Greece.

RESUMEN / SUMMARY: - Colorectal cancer (CRC) is the third most common type of cancer and is responsible for 9 % of cancer deaths in both men and women in the USA for 2013. It is a heterogenous disease, and its three classification types are microsatellite instability, chromosomal instability, and CpG island methylator phenotype. Biomarkers are molecules, which can be used as indicators of cancer. They have the potential to achieve great sensitivities and specificities in diagnosis and prognosis of CRC. DNA methylation biomarkers are epigenetic markers, more specifically genes that become silenced after aberrant methylation of their promoter in CRC. Some methylation biomarkers like SEPT9 (ColoVantage®) and vimentin (ColoSure™) are already commercially available. Other blood and fecal-based biomarkers are currently under investigation and clinical studies so that they can be used in the near future. Biomarker panels are also currently being studied since they show great potential in diagnosis as they can combine robust biomarkers to achieve even greater sensitivities than single markers. Finally, methylation-sensitive microRNAs (miRNAs) are very promising markers, and their investigation as biomarkers, is only at primitive stage.

[1041]

TÍTULO / TITLE: - Use of ACE Inhibitors and Angiotensin Receptor Blockers and Primary Breast Cancer Outcomes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cancer. 2013 Aug 10;4(7):549-56. doi: 10.7150/jca.6888.

●● Enlace al texto completo (gratis o de pago) [7150/jca.6888](#)

AUTORES / AUTHORS: - Chae YK; Brown EN; Lei X; Melhem-Bertrandt A; Giordano SH; Litton JK; Hortobagyi GN; Gonzalez-Angulo AM; Chavez-Macgregor M

INSTITUCIÓN / INSTITUTION: - 1. Division of Cancer Medicine.

RESUMEN / SUMMARY: - BACKGROUND: ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may have anti-tumor properties. We investigated whether the use of ACEI/ARBs affects the clinical outcomes of primary breast cancer patients receiving taxane and anthracycline-based neoadjuvant chemotherapy. METHODS: We included 1449 patients with diagnosis of invasive primary breast cancer diagnosed at the MD Anderson Cancer Center between 1995 and 2007 who underwent neoadjuvant chemotherapy. Of them, 160 (11%) patients were identified by review of their medical

record, as ACEI/ARBs users. We compared pathologic complete response (pCR) rates, relapse-free survival (RFS), disease-specific survival (DSS) and overall survival (OS) between ACEI/ARB users and non-users. Descriptive statistics and Cox proportional hazards model were used in the analyses. RESULTS: There was no difference in the pCR rates between ACEI/ARB users and non-users (16% vs 18.1%, $p=0.50$). After adjustment for important demographic and clinical characteristics, no significant differences between ACEI/ARB users and nonusers were observed in RFS (HR=0.81; 95% CI=0.54-1.21), DSS (HR=0.83; 95% CI=0.52-1.31), or OS (HR=0.91; 95% CI =0.61-1.37). In a subgroup analysis, the 5-year RFS was 82% in ARB only users versus 71% in ACEI/ARB non-users ($P=0.03$). In the multivariable analysis, ARB use was also associated with a decreased risk of recurrence (HR=0.35; 95% CI=0.14-0.86). No statistically significant differences in DSS or OS were seen. CONCLUSION: No differences in pCR and survival outcomes were seen between ACEI/ARB users and non-users among breast cancer patients receiving neoadjuvant chemotherapy. ARB use may be associated with improved RFS. Further research is needed to validate this finding.

[1042]

TÍTULO / TITLE: - The effect of interleukin-2 on canine peripheral nerve sheath tumours after marginal excision: a double-blind randomized study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Vet Res. 2013 Aug 8;9(1):155.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1746-6148-9-155](#)

AUTORES / AUTHORS: - Haagsman AN; Witkamp AC; Sjollema BE; Kik MJ; Kirpensteijn J

RESUMEN / SUMMARY: - BACKGROUND: The objective of this study was to evaluate the effect on outcomes of intraoperative recombinant human interleukin-2 injection after surgical resection of peripheral nerve sheath tumours. In this double-blind trial, 40 patients due to undergo surgical excision (<5 mm margins) of presumed peripheral nerve sheath tumours were randomized to receive intraoperative injection of interleukin-2 or placebo into the wound bed. RESULTS: There were no significant differences in any variable investigated or in median survival between the two groups. The median recurrence free interval was 874 days (range 48--2141 days), The recurrence-free interval and overall survival time were significantly longer in dogs that undergone the primary surgery by a specialist-certified surgeon compared to a referring veterinarian regardless of whether additional adjunct therapy was given. CONCLUSION: Overall, marginal excision of peripheral nerve sheath tumours in dogs resulted in a long survival time, but adjuvant treatment with recombinant human interleukin-2 (rhIL-2) did not provide a survival advantage.

[1043]

TÍTULO / TITLE: - KLF4 expression and apoptosis-related markers in gastric cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J BUON. 2013 Jul-Sep;18(3):695-702.

AUTORES / AUTHORS: - Krstic M; Stojnev S; Jovanovic L; Marjanovic G

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Faculty of Medicine, University of Nis, Nis, Serbia.

RESUMEN / SUMMARY: - Purpose: To correlate the expression of Kruppel-like factor 4 (KLF4) with clinicopathological properties of gastric cancer (GC) and to evaluate any possible correlation between KLF4 expression and the expression of apoptosis-related markers p53, Fas, Bcl-2, survivin and FLICE inhibitory protein (Flip-I). Methods: Formalin-fixed, paraffin-embedded tissue specimens obtained from 96 patients with GC who had undergone gastric surgery were analyzed for pathological parameters, while KLF4, p53, Fas, Bcl-2, survivin and Flip-I expression was assessed by immunohistochemistry. Results: TKLF4 immunohistochemical staining was noted in 78.1% of the cases. Strong positivity was found in 15.6% and weak in 62.5% of the samples. Positive expression of p53, Fas, Bcl-2, survivin, Flip-I was found in 56.2%, 44.8%, 15.6%, 41.7% and 38.5% of the samples, respectively. KLF4 expression was significantly associated with p53 nuclear staining and Fas immunoreactivity. p53-positive tumors demonstrated more often high KLF4 staining compared to p53-negative tumors. Fas-positive tumors were associated with decreased KLF4 expression. Logistic regression analysis of apoptosis-related markers to KLF4 expression revealed that Fas positivity significantly decreased the probability of strong KLF4 expression, and inversely, Bcl-2 expression improved the prediction of KLF4 staining. When all 5 predictive variables were considered together (p53, Fas, survivin, Bcl-2, Flip-I) they significantly predicted the type of KLF4 expression in GC cells (p=0.019). Conclusion: Our results suggest that the decrease or loss of KLF4 expression correlates with diffuse-type GC and immunoreactivity to Fas, and are inversely linked with p53 nuclear accumulation. The significance of KLF4 in GC requires further studies and should be more thoroughly investigated for potential use in the evaluation and better stratification of GC patients.

[1044]

TÍTULO / TITLE: - The Value of Somatostatin Receptor Imaging with In-111 Octreotide and/or Ga-68 DOTATATE in Localizing Ectopic ACTH Producing Tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Imaging Radionucl Ther. 2013 Aug;22(2):49-55. doi: 10.4274/Mirt.69775. Epub 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [4274/Mirt.69775](#)

AUTORES / AUTHORS: - Gozde Ozkan Z; Kuyumcu S; Balkose D; Ozkan B; Aksakal N; Yilmaz E; Sanli Y

INSTITUCIÓN / INSTITUTION: - Istanbul University Istanbul Medical Faculty, Nuclear Medicine Department, Istanbul, Turkey.

RESUMEN / SUMMARY: - Objective: We aimed to evaluate the value of somatostatin receptor imaging (SRI) with In-111 octreotide and Ga-68 DOTATATE in localizing ectopic ACTH producing tumors. Methods: Nineteen patients who had In-111 octreotide somatostatin receptor scintigraphy (SRS) and/or Ga-68 DOTATATE PET-CT to localize ectopic ACTH producing tumors between the years 2000 and 2012 were included retrospectively in our study. The results of SRI were compared with clinical onset, radiological findings and surgical data of the patients. Results: Sixteen In-111 octreotide SRS and five Ga-68 DOTATATE PET-CT were performed in 19 patients. In eight out of 19 patients, ectopic ACTH secretion site could be detected. In five patients, SRS showed pathologic uptake. In four of these patients, surgery revealed pulmonary carcinoid tumors and in one patient pancreatic neuroendocrine tumor. In one patient, Ga-68 DOTATATE PET-CT revealed pathologic uptake in lung nodule which came out to be pulmonary carcinoid tumor. In another patient who had resection of metastases of atypical carcinoid tumor prior to scans, new metastatic foci were detected both with SRS and Ga-68 DOTATATE PET-CT imaging. In one patient, although SRS was negative, CT which was performed three years later showed a lung nodule diagnosed as pulmonary carcinoid tumor. In 11 patients, ectopic ACTH secretion site could not be detected. In 10 of those patients, scintigraphic and radiological imaging did not show any lesions and in one patient, Ga-68 DOTATATE PET-CT was false positive. Conclusion: SRI has a complementary role with radiological imaging in localizing ectopic ACTH secretion sites. PET-CT imaging with Ga-68 peptide conjugates is a promising new modality for this indication. Conflict of interest:None declared.

[1045]

TÍTULO / TITLE: - Ribonucleotide reductase large subunit M1 predicts poor survival due to modulation of proliferative and invasive ability of gastric cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e70191. doi: 10.1371/journal.pone.0070191. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070191](#)

AUTORES / AUTHORS: - Wang Q; Liu X; Zhou J; Huang Y; Zhang S; Shen J; Loera S; Yuan X; Chen W; Jin M; Shibata S; Liu Y; Chu P; Wang L; Yen Y

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology, Affiliated Sir Runrun Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China.

RESUMEN / SUMMARY: - OBJECTIVES: We aimed to investigate the prognostic value of RRM1 in GC patients. METHODS: A total of assessable 389 GC patients with clinicopathological and survival information were enrolled from City of Hope (COH, n = 67) and Zhejiang University (ZJU, n = 322). RRM1 protein expression was determined by immunohistochemistry on FFPE tissue samples. Kaplan-Meier and Cox analyses were used to measure survival. Ras/Raf activity and invasion assays were used to evaluate the role of RRM1 in GC cell lines. RESULTS: In vitro experiments demonstrated

RRM1 activated Ras/Raf/MAPK signal transduction and promoted GC cell proliferation. Meanwhile, RRM1 expression was significantly associated with lymph node involvement, tumor size, Ki67 expression, histological subtype and histological grade in the GC tissue samples ($p < 0.05$). Kaplan-Meier analysis illustrated that high RRM1 expression predicted poor survival in GC patients in the COH and ZJU cohorts (log-rank $p < 0.01$). In multivariate Cox analysis, the hazard ratios of RRM1 for overall survival were 2.55 (95% CI 1.27-5.15) and 1.51 (95% CI 1.07-2.13) in the COH and ZJU sets, respectively. In particular, RRM1 specifically predicted the outcome of advanced GCs with poor differentiation and high proliferative ability. Furthermore, inhibition of RRM1 by siRNA significantly reduced the dNTP pool, Ras/Raf and MMP-9 activities and the levels of p-MEK, p-ERK and NF- κ B, resulting in growth retardation and reduced invasion in AGS and NCI-N87 cells. CONCLUSIONS: RRM1 overexpression predicts poor survival in GC patients with advanced TNM stage. RRM1 could potentially serve as prognostic biomarker and therapeutic target for GCs.

[1046]

TÍTULO / TITLE: - Estradiol and Tamoxifen Induce Cell Migration through GPR30 and Activation of Focal Adhesion Kinase (FAK) in Endometrial Cancers with Low or without Nuclear Estrogen Receptor alpha (ERalpha).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 9;8(9):e72999. doi: 10.1371/journal.pone.0072999.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072999](#)

AUTORES / AUTHORS: - Tsai CL; Wu HM; Lin CY; Lin YJ; Chao A; Wang TH; Hsueh S; Lai CH; Wang HS

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Lin-Kou Medical Center, Chang Gung University, Taoyuan, Taiwan ; Genomic Medicine Research Core Laboratory, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

RESUMEN / SUMMARY: - Estrogens and tamoxifen (an antiestrogen) exert their actions by activation of estrogen receptor (ER) through genomic and non-genomic mechanisms and are implicated in the development of endometrial cancer. Previous reports have demonstrated that estradiol and tamoxifen induce proliferation of human endometrial cancer cells through GPR30 (non-genomic ER) signaling pathway. Herein, we demonstrate that phosphorylation of focal adhesion kinase (FAK) is involved in cell migration induced by estradiol, tamoxifen and G1 (a GPR30 agonist) through the transmembrane ER (GPR30) in endometrial cancer cell lines with or without ERalpha (Ishikawa and RL95-2). Additionally, the GPR30-mediated cell migration was further abolished by administration of either specific RNA interference targeting GPR30 or an FAK inhibitor. Moreover, we have validated that the signaling between GPR30 and phosphorylated FAK is indeed mediated by the EGFR/PI3K/ERK pathway. Clinically, a

significant correlation between levels of GPR30 and phosphorylated FAK (pFAK) observed in human endometrial cancer tissues with low or without ERalpha further suggested that estrogen-induced phosphorylation of FAK and cell migration were most likely triggered by GPR30 activation. These results provided new insights for understanding the pathophysiological functions of GPR30 in human endometrial cancers.

[1047]

TÍTULO / TITLE: - Geldanamycin-induced osteosarcoma cell death is associated with hyperacetylation and loss of mitochondrial pool of heat shock protein 60 (hsp60).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 28;8(8):e71135. doi: 10.1371/journal.pone.0071135.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071135](#)

AUTORES / AUTHORS: - Gorska M; Marino Gammazza A; Zmijewski MA; Campanella C; Cappello F; Wasiewicz T; Kuban-Jankowska A; Daca A; Sielicka A; Popowska U; Knap N; Antoniewicz J; Wakabayashi T; Wozniak M

INSTITUCIÓN / INSTITUTION: - Department of Medical Chemistry, Medical University of Gdansk, Gdansk, Poland.

RESUMEN / SUMMARY: - Osteosarcoma is one of the most malignant tumors of childhood and adolescence that is often resistant to standard chemo- and radio-therapy. Geldanamycin and geldanamycin analogs have been recently studied as potential anticancer agents for osteosarcoma treatment. Here, for the first time, we have presented novel anticancer mechanisms of geldanamycin biological activity. Moreover, we demonstrated an association between the effects of geldanamycin on the major heat shock proteins (HSPs) and the overall survival of highly metastatic human osteosarcoma 143B cells. We demonstrated that the treatment of 143B cells with geldanamycin caused a subsequent upregulation of cytoplasmic Hsp90 and Hsp70 whose activity is at least partly responsible for cancer development and drug resistance. On the other hand, geldanamycin induced upregulation of Hsp60 gene expression, and a simultaneous loss of hyperacetylated Hsp60 mitochondrial protein pool resulting in decreased viability and augmented cancer cell death. Hyperacetylation of Hsp60 seems to be associated with anticancer activity of geldanamycin. In light of the fact that mitochondrial dysfunction plays a critical role in the apoptotic signaling pathway, the presented data may support a hypothesis that Hsp60 can be another functional part of mitochondria-related acetylome being a potential target for developing novel anticancer strategies.

[1048]

TÍTULO / TITLE: - Kinesin spindle protein inhibitors in cancer: a patent review (2008 - present).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Opin Ther Pat. 2013 Aug 26.

●● Enlace al texto completo (gratis o de pago) [1517/13543776.2013.833606](#)

AUTORES / AUTHORS: - Jiang C; You Q

INSTITUCIÓN / INSTITUTION: - China Pharmaceutical University, Department of Medicinal Chemistry and Jiangsu Key Laboratory of Carcinogenesis and Intervention, Jiangsu Key Laboratory of Drug Design and Optimization, Nanjing 210009, China.

RESUMEN / SUMMARY: - Introduction: Inhibition of kinesin spindle protein (KSP) has emerged as a novel and validated therapeutic strategy against cancers. A lot of new KSP inhibitors have been identified in recent years and some of them have entered clinical trials. This may provide more selections in future cancer therapy. Areas covered: In the present review, the authors will describe the most recent classes of KSP inhibitors by reviewing about 96 literatures in which 24 patent applications were included from 2008 to now. Expert opinion: Many new KSP inhibitors have been discovered that act either by binding in an allosteric site of KSP or by ATP competitive inhibition. There are several ATP non-competitive KSP inhibitors entering clinical investigation. Although they were both well tolerated and showed acceptable pharmacokinetic profiles, limited clinical response was always the problem. Mutation of the binding pocket was also a hindrance in the development of these allosteric inhibitors. The appearance of ATP competitive KSP inhibitors was considered to be able to overcome mutation-mediated resistance to the allosteric inhibitors, which could be a new approach for the development of novel KSP inhibitors.

[1049]

TÍTULO / TITLE: - Structure and Inducing Tumor Cell Apoptosis Activity of Polysaccharides Isolated from *Lentinus edodes*.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Agric Food Chem. 2013 Sep 25.

●● Enlace al texto completo (gratis o de pago) [1021/jf403291w](#)

AUTORES / AUTHORS: - Wang KP; Zhang QL; Liu Y; Wang J; Cheng Y; Zhang Y

RESUMEN / SUMMARY: - In this study, five novel polysaccharides SLNT1, SLNT2, JLNT1, JLNT2 and JLNT3 were isolated from the fruit body of *Lentinus edodes*. Chemical and physical analyses showed that the five polysaccharides consist of glucose with the structure of beta-(1->3)-D-glucose main chains and beta-(1->6)-D-glucose side chains. Moreover, all of them had triple-helical conformation and different molecular weight distributions. Animal studies further demonstrated that the antitumor effects were remarkably improved by SLNT1 and JLNT1 treatments with the inhibitory rates of 56.25% and 68.16% in H22-bearing mice respectively. Additionally, both of them significantly increased the levels of serum IL-2 and TNF-alpha production, and induced the tumor cell apoptosis. Taken together, our findings revealed that the involved antitumor mechanisms possibly in part were mediated not only by enhancing the

immunity, but also by directly killing tumor and the induction of tumor cell apoptosis in H22-bearing-mice.

[1050]

TÍTULO / TITLE: - Genetic aberrations in imatinib-resistant dermatofibrosarcoma protuberans revealed by whole genome sequencing.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e69752. doi: 10.1371/journal.pone.0069752. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069752](https://doi.org/10.1371/journal.pone.0069752)

AUTORES / AUTHORS: - Hong JY; Liu X; Mao M; Li M; Choi DI; Kang SW; Lee J; La Choi Y

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - Dermatofibrosarcoma protuberans (DFSP) is a very rare soft tissue sarcoma. DFSP often reveals a specific chromosome translocation, t(17;22)(q22;q13), which results in the fusion of collagen 1 alpha 1 (COL1A1) gene and platelet-derived growth factor-B (PDGFB) gene. The COL1A1-PDGFB fusion protein activates the PDGFB receptor and resultant constitutive activation of PDGFR receptor is essential in the pathogenesis of DFSP. Thus, blocking PDGFR receptor activation with imatinib has shown promising activity in the treatment of advanced and metastatic DFSP. Despite the success with targeted agents in cancers, acquired drug resistance eventually occurs. Here, we tried to identify potential drug resistance mechanisms against imatinib in a 46-year old female with DFSP who initially responded well to imatinib but suffered rapid disease progression. We performed whole-genome sequencing of both pre-treatment and post-treatment tumor tissue to identify the mutational events associated with imatinib resistance. No significant copy number alterations, insertion, and deletions were identified during imatinib treatment. Of note, we identified newly emerged 8 non-synonymous somatic mutations of the genes (ACAP2, CARD10, KIAA0556, PAAQR7, PPP1R39, SAFB2, STARD9, and ZFYVE9) in the imatinib-resistant tumor tissue. This study revealed diverse possible candidate mechanisms by which imatinib resistance to PDGFRB inhibition may arise in DFSP, and highlights the usefulness of whole-genome sequencing in identifying drug resistance mechanisms and in pursuing genome-directed, personalized anti-cancer therapy.

[1051]

TÍTULO / TITLE: - Combination of siRNA-directed Gene Silencing With Cisplatin Reverses Drug Resistance in Human Non-small Cell Lung Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Ther Nucleic Acids. 2013 Jul 30;2:e110. doi: 10.1038/mtna.2013.29.

●● Enlace al texto completo (gratis o de pago) [1038/mtna.2013.29](https://doi.org/10.1038/mtna.2013.29)

AUTORES / AUTHORS: - Ganesh S; Iyer AK; Weiler J; Morrissey DV; Amiji MM

INSTITUCIÓN / INSTITUTION: - 1] Department of Pharmaceutical Sciences, School of Pharmacy, Bouve College of Health Sciences, Northeastern University, Boston, Massachusetts, USA [2] Novartis Institutes for Biomedical Research Inc., Cambridge, Massachusetts, USA.

RESUMEN / SUMMARY: - One of the most challenging aspects of lung cancer therapy is the rapid acquisition of multidrug-resistant (MDR) phenotype. One effective approach would be to identify and downregulate resistance-causing genes in tumors using small interfering RNAs (siRNAs) to increase the sensitivity of tumor cells to chemotherapeutic challenge. After identifying the overexpressed resistance-related antiapoptotic genes (survivin and bcl-2) in cisplatin-resistant cells, the siRNA sequences were designed and screened to select the most efficacious candidates. Modifications were introduced in them to minimize off-target effects. Subsequently, the combination of siRNA and cisplatin that gave the maximum synergy was identified in resistant cells. We then demonstrated that the combination treatment of the selected siRNAs and cisplatin encapsulated in CD44-targeting hyaluronic acid (HA)-based self-assembling nanosystems reversed the resistance to cisplatin and delayed the tumor growth significantly (growth inhibition increased from 30 to 60%) in cisplatin-resistant tumors. In addition, no abnormalities in body weights, liver enzyme levels or histopathology of liver/spleen tissues were observed in any of the treatment groups during the study period. Overall, we demonstrate that the combination of siRNA-mediated gene-silencing strategy with chemotherapeutic agents constitutes a valuable and safe approach for the treatment of MDR tumors. *Molecular Therapy-Nucleic Acids* (2013) 2, e110; doi:10.1038/mtna.2013.29; published online 30 July 2013.

[1052]

TÍTULO / TITLE: - In vitro regulation of hepatocellular carcinoma cell viability, apoptosis, invasion, and AEG-1 expression by LY294002.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Clin Res Hepatol Gastroenterol.* 2013 Jul 30. pii: S2210-7401(13)00142-3. doi: 10.1016/j.clinre.2013.06.012.

●● Enlace al texto completo (gratis o de pago) [1016/j.clinre.2013.06.012](https://doi.org/10.1016/j.clinre.2013.06.012)

AUTORES / AUTHORS: - Ma J; Xie SL; Geng YJ; Jin S; Wang GY; Lv GY

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary and Pancreatic Surgery, The First Norman Bethune Hospital of Jilin University, Changchun 130021, China.

[1053]

TÍTULO / TITLE: - DEK over expression as an independent biomarker for poor prognosis in colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 31;13:366. doi: 10.1186/1471-2407-13-366.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-366](https://doi.org/10.1186/1471-2407-13-366)

AUTORES / AUTHORS: - Lin L; Piao J; Gao W; Piao Y; Jin G; Ma Y; Li J; Lin Z

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Yanbian University College of Medicine, Yanji 133002, China.

RESUMEN / SUMMARY: - BACKGROUND: The DEK protein is related to chromatin reconstruction and gene transcription, and plays an important role in cell apoptosis. High expression levels of the human DEK gene have been correlated with numerous human malignancies. This study explores the roles of DEK in tumor progression and as a prognostic determinant of colorectal cancer. METHODS: Colorectal cancer specimens from 109 patients with strict follow-up, and colorectal adenomas from 52 patients were selected for analysis of DEK protein by immunohistochemistry. The correlations between DEK over expression and the clinicopathological features of colorectal cancers were evaluated by Chi-square test and Fisher's exact tests. The survival rates were calculated by the Kaplan-Meier method, and the relationship between prognostic factors and patient survival was also analyzed by the Cox proportional hazard models. RESULTS: DEK protein showed a nuclear immunohistochemical staining pattern in colorectal cancers. The strongly positive rate of DEK protein was 48.62% (53/109) in colorectal cancers, which was significantly higher than that in either adjacent normal colon mucosa (9.17%, 10/109) or colorectal adenomas (13.46%, 7/52). DEK over expression in colorectal cancers was positively correlated with tumor size, grade, lymph node metastasis, serosal invasion, late stage, and disease-free survival- and 5-year survival rates. Further analysis showed that patients with late stage colorectal cancer and high DEK expression had worse survival rates than those with low DEK expression. Moreover, multivariate analysis showed high DEK expression, serosal invasion, and late stage are significant independent risk factors for mortality in colorectal cancer. CONCLUSIONS: DEK plays an important role in the progression of colorectal cancers and it is an independent poor prognostic factor of colorectal cancers.

[1054]

TÍTULO / TITLE: - Anti-androgen receptor ASC-J9 versus anti-androgens MDV3100 (Enzalutamide) or Casodex (Bicalutamide) leads to opposite effects on prostate cancer metastasis via differential modulation of macrophage infiltration and STAT3-CCL2 signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 8;4:e764. doi: 10.1038/cddis.2013.270.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.270](https://doi.org/10.1038/cddis.2013.270)

AUTORES / AUTHORS: - Lin TH; Izumi K; Lee SO; Lin WJ; Yeh S; Chang C

INSTITUCIÓN / INSTITUTION: - George Whipple Lab for Cancer Research, University of Rochester Medical Center, Rochester, NY 14642, USA.

RESUMEN / SUMMARY: - Despite androgen deprivation therapy (ADT) suppression of prostate cancer (PCa) growth, its overall effects on PCa metastasis remain unclear. Using human (C4-2B/THP1) and mouse (TRAMP-C1/RAW264.7) PCa cells-macrophages co-culture systems, we found currently used anti-androgens, MDV3100 (enzalutamide) or Casodex (bicalutamide), promoted macrophage migration to PCa cells that consequently led to enhanced PCa cell invasion. In contrast, the AR degradation enhancer, ASC-J9, suppressed both macrophage migration and subsequent PCa cell invasion. Mechanism dissection showed that Casodex/MDV3100 reduced the AR-mediated PIAS3 expression and enhanced the pSTAT3-CCL2 pathway. Addition of CCR2 antagonist reversed the Casodex/MDV3100-induced macrophage migration and PCa cell invasion. In contrast, ASC-J9 could regulate pSTAT3-CCL2 signaling using two pathways: an AR-dependent pathway via inhibiting PIAS3 expression and an AR-independent pathway via direct inhibition of the STAT3 phosphorylation/activation. These findings were confirmed in the in vivo mouse model with orthotopically injected TRAMP-C1 cells. Together, these results may raise the potential concern about the currently used ADT with anti-androgens that promotes PCa metastasis and may provide some new and better therapeutic strategies using ASC-J9 alone or a combinational therapy that simultaneously targets androgens/AR signaling and PIAS3-pSTAT3-CCL2 signaling to better battle PCa growth and metastasis at castration-resistant stage.

[1055]

TÍTULO / TITLE: - Human voltage-gated proton channel hv1: a new potential biomarker for diagnosis and prognosis of colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 5;8(8):e70550. doi: 10.1371/journal.pone.0070550. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070550](https://doi.org/10.1371/journal.pone.0070550)

AUTORES / AUTHORS: - Wang Y; Wu X; Li Q; Zhang S; Li SJ

INSTITUCIÓN / INSTITUTION: - Department of Biophysics, School of Physics Science, Nankai University, Tianjin, China ; Department of Pathology, Tonghua Center Hospital, Tonghua, China.

RESUMEN / SUMMARY: - Solid tumors exist in a hypoxic microenvironment, and possess high-glycolytic metabolites. To avoid the acidosis, tumor cells must exhibit a dynamic cytosolic pH regulation mechanism(s). The voltage-gated proton channel Hv1 mediates NADPH oxidase function by compensating cellular loss of electrons with protons. Here, we showed for the first time, that Hv1 expression is increased in colorectal tumor tissues and cell lines, associated with poor prognosis. Immunohistochemistry showed that Hv1 is strongly expressed in adenocarcinomas but not or lowly expressed in normal colorectal or hyperplastic polyps. Hv1 expression in colorectal cancer is significantly associated with the tumor size, tumor classification,

lymph node status, clinical stage and p53 status. High Hv1 expression is associated significantly with shorter overall and recurrence-free survival. Furthermore, real-time RT-PCR and immunocytochemistry showed that Hv1 is highly expressed in colorectal cancer cell lines, SW620, HT29, LS174T and Colo205, but not in SW480. Inhibitions of Hv1 expression and activity in the highly metastatic SW620 cells by small interfering RNA (siRNA) and Zn(2+) respectively, markedly decrease the cell invasion and migration, restraint proton extrusion and the intracellular pH recovery. Our results suggest that Hv1 may be used as a potential biomarker for diagnosis and prognosis of colorectal carcinoma, and a potential target for anticancer drugs in colorectal cancer therapy.

[1056]

TÍTULO / TITLE: - Predictive Value of XPD Polymorphisms on Platinum-Based Chemotherapy in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 19;8(8):e72251. doi: 10.1371/journal.pone.0072251.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072251](#)

AUTORES / AUTHORS: - Qiu M; Yang X; Hu J; Ding X; Jiang F; Yin R; Xu L

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Institute of Jiangsu Province, Nanjing, China ; The Fourth Clinical College of Nanjing Medical University, Nanjing, China.

RESUMEN / SUMMARY: - BACKGROUND: The correlation between xeroderma pigmentosum group D (XPD) polymorphisms (Lys751Gln and Asp312Asn) and clinical outcomes of non-small cell lung cancer (NSCLC) patients, who received platinum-based chemotherapy (Pt-chemotherapy), is still inconclusive. This meta-analysis was aimed to systematically review published evidence and ascertain the exact role of XPD polymorphisms. METHODS: Databases of MEDLINE and EMBASE were searched up to April 2013 to identify eligible studies. A rigorous quality assessment of eligible studies was conducted according to the Newcastle-Ottawa Quality Assessment Scales. The relationship between XPD polymorphisms and response to Pt-chemotherapy and survival was analyzed. RESULTS: A total of 22 eligible studies were included and analyzed in this meta-analysis. The overall analysis suggested that the XPD Lys751Gln polymorphism was not associated with response to Pt-chemotherapy or survival. However, the XPD 312Asn allele was significantly associated with poor response to Pt-chemotherapy compared with the Asp312 allele (Asn vs. Asp: OR = 0.435, 95% CI: 0.261-0.726). Additionally, the variant genotype of XPD Asp312Asn polymorphism was associated with favorable survival in Caucasian (AspAsn vs. AspAsp: HR = 0.781, 95% CI: 0.619-0.986) but unfavorable survival in Asian (AspAsn+AsnAsn vs. AspAsp: HR = 1.550, 95% CI: 1.038-2.315). CONCLUSIONS: These results suggest that XPD Asp312Asn

polymorphism may function as a predictive biomarker on platinum-based chemotherapy in NSCLC and further studies are warranted.

[1057]

TÍTULO / TITLE: - Induction of a feed forward pro-apoptotic mechanistic loop by nitric oxide in a human breast cancer model.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013;8(8):e70593. doi: 10.1371/journal.pone.0070593.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070593](#)

AUTORES / AUTHORS: - Sen S; Kawahara B; Fukuto J; Chaudhuri G

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California, United States of America.

RESUMEN / SUMMARY: - We have previously demonstrated that relatively high concentrations of NO [Nitric Oxide] as produced by activated macrophages induced apoptosis in the human breast cancer cell line, MDA-MB-468. More recently, we also demonstrated the importance of endogenous H₂O₂ in the regulation of growth in human breast cancer cells. In the present study we assessed the interplay between exogenously administered NO and the endogenously produced reactive oxygen species [ROS] in human breast cancer cells and evaluated the mechanism[s] in the induction of apoptosis. To this end we identified a novel mechanism by which NO down regulated endogenous hydrogen peroxide [H₂O₂] formation via the down-regulation of superoxide [O₂ (-)] and the activation of catalase. We further demonstrated the existence of a feed forward mechanistic loop involving protein phosphatase 2^a [PP2A] and its downstream substrate FOXO1 in the induction of apoptosis and the synthesis of catalase. We utilized gene silencing of PP2A, FOXO1 and catalase to assess their relative importance and key roles in NO mediated apoptosis. This study provides the potential for a therapeutic approach in treating breast cancer by targeted delivery of NO where NO donors and activators of downstream players could initiate a self sustaining apoptotic cascade in breast cancer cells.

[1058]

TÍTULO / TITLE: - V-ATPase inhibition overcomes trastuzumab resistance in breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Oncol. 2013 Sep 5. pii: S1574-7891(13)00122-1. doi: 10.1016/j.molonc.2013.08.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.molonc.2013.08.011](#)

AUTORES / AUTHORS: - von Schwarzenberg K; Lajtos T; Simon L; Muller R; Vereb G; Vollmar AM

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Pharmaceutical Biology, Ludwig-Maximilians-University Munich, Butenandtstr. 5-13, 81377 Munich, Germany.
Electronic address: karin.von.schwarzenberg@cup.uni-muenchen.de.

RESUMEN / SUMMARY: - The HER2 oncogene targeting drug trastuzumab shows remarkable efficacy in patients overexpressing HER2. However acquired or primary resistance develops in most of the treated patients why alternative treatment strategies are strongly needed. As endosomal sorting and recycling are crucial steps for HER2 activity and the vacuolar H⁺-ATPase (V-ATPase) is an important regulator of endocytotic trafficking, we proposed that targeting V-ATPase opens a new therapeutic strategy against trastuzumab-resistant tumor cells in vitro and in vivo. V-ATPase inhibition with archazolid, a novel inhibitor of myxobacterial origin, results in growth inhibition, apoptosis and impaired HER2 pro-survival signaling of the trastuzumab-resistant cell line JIMT-1. This is accompanied by a decreased expression on the plasma membrane and accumulation of HER2 in the cytosol, where it colocalizes with endosomes, lysosomes and autophagosomes. Importantly, microscopic analysis of JIMT-1 xenograft tumor tissue of archazolid treated mice confirms the defect in HER2-recycling which leads to reduced tumor growth. These results suggest that V-ATPase inhibition by archazolid induces apoptosis and inhibits growth of trastuzumab-resistant tumor cells by retaining HER2 in dysfunctional vesicles of the recycling pathway and consequently abrogates HER2-signaling in vitro as well as in vivo. V-ATPase inhibition is thus suggested as a promising strategy for treatment of trastuzumab-resistant tumors.

[1059]

TÍTULO / TITLE: - Sonic Hedgehog Promotes Tumor Cell Survival by Inhibiting CDON Pro-Apoptotic Activity.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS Biol. 2013 Aug;11(8):e1001623. doi: 10.1371/journal.pbio.1001623. Epub 2013 Aug 6.

●● Enlace al texto completo (gratuito o de pago) [1371/journal.pbio.1001623](https://doi.org/10.1371/journal.pbio.1001623)

AUTORES / AUTHORS: - Delloye-Bourgeois C; Gibert B; Rama N; Delcros JG; Gadot N; Scoazec JY; Krauss R; Bernet A; Mehlen P

INSTITUCIÓN / INSTITUTION: - Apoptosis, Cancer and Development Laboratory-Equipe labellisee 'La Ligue', LabEx DEVweCAN, Centre de Cancerologie de Lyon, Institut National de la Sante et de la Recherche Medicale (INSERM) U1052- Centre National de la Recherche Scientifique (CNRS) Unite Mixte de Recherche (UMR5286), Universite de Lyon, Centre Leon Berard, 69008 Lyon, France.

RESUMEN / SUMMARY: - The Hedgehog signaling is a determinant pathway for tumor progression. However, while inhibition of the Hedgehog canonical pathway-Patched-Smoothed-Gli-has proved efficient in human tumors with activating mutations in this pathway, recent clinical data have failed to show any benefit in other cancers, even though Sonic Hedgehog (SHH) expression is detected in these cancers. Cell-

adhesion molecule-related/down-regulated by Oncogenes (CDON), a positive regulator of skeletal muscle development, was recently identified as a receptor for SHH. We show here that CDON behaves as a SHH dependence receptor: it actively triggers apoptosis in the absence of SHH. The pro-apoptotic activity of unbound CDON requires a proteolytic cleavage in its intracellular domain, allowing the recruitment and activation of caspase-9. We show that by inducing apoptosis in settings of SHH limitation, CDON expression constrains tumor progression, and as such, decreased CDON expression observed in a large fraction of human colorectal cancer is associated in mice with intestinal tumor progression. Reciprocally, we propose that the SHH expression, detected in human cancers and previously considered as a mechanism for activation of the canonical pathway in an autocrine or paracrine manner, actually provides a selective tumor growth advantage by blocking CDON-induced apoptosis. In support of this notion, we present the preclinical demonstration that interference with the SHH-CDON interaction triggers a CDON-dependent apoptosis in vitro and tumor growth inhibition in vivo. The latter observation qualifies CDON as a relevant alternative target for anticancer therapy in SHH-expressing tumors.

[1060]

TÍTULO / TITLE: - Resistance to cancer in amphibians: a role for apoptosis?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Altern Lab Anim. 2013 Jul;41(3):231-4.

AUTORES / AUTHORS: - Ruben LN; Johnson RO; Clothier RH; Balls M

INSTITUCIÓN / INSTITUTION: - Reed College, Portland, OR, USA. ruben@reed.edu

RESUMEN / SUMMARY: - The rarity of spontaneous cancer in amphibians, and the difficulty of inducing cancer in these lower vertebrates, suggest that they possess an effective system for resistance to the development of cancer. The first part of this narrative presents evidence for cancer resistance in amphibians, and then a variety of studies designed to help understand the physiological basis for this resistance are reviewed. Here, our emphasis is on evidence with regard to the role that apoptosis might play.

[1061]

TÍTULO / TITLE: - Detection of novel paraja ring finger 2-fer tyrosine kinase mRNA chimeras is associated with poor postoperative prognosis in non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Sci. 2013 Aug 12. doi: 10.1111/cas.12250.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cas.12250](#)

AUTORES / AUTHORS: - Kawakami M; Ishikawa R; Amano Y; Sunohara M; Watanabe K; Ohishi N; Yatomi Y; Nakajima J; Fukayama M; Nagase T; Takai D

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The University of Tokyo Hospital, Tokyo, Japan; Department of Clinical Laboratory, The University of Tokyo Hospital, Tokyo, Japan.

RESUMEN / SUMMARY: - Previously, we reported that the overexpression of fer tyrosine kinase (FER), a non-receptor tyrosine kinase, is correlated with poor postoperative prognosis and cancer-cell survival in non-small cell lung cancer (NSCLC). In the present study, we further analyzed FER-overexpressed NSCLC cases and identified various patterns of chimeric mRNAs, composed of paraja ring finger 2 (PJA2) and FER. We detected no genomic rearrangements between PJA2 and FER and attributed these chimeric mRNAs to alterations at the transcriptome level: i.e., trans-splicing. Several chimeric patterns were detected concurrently in each patient, and the pattern sets varied among patients, although the pattern in which PJA2 exon 1 was fused to FER exon 3 (designated as Pe1-Fe3 mRNA) was detected constantly. Therefore, in a wide screening for PJA2-FER mRNAs in NSCLC, we focused on this chimeric pattern as a representative chimera. In analyses of 167 NSCLC samples, Pe1-Fe3 mRNA was identified in about 10% of the patients, and the presence of chimeric mRNA was significantly correlated with a high expression level of parental FER mRNA. Furthermore, we found that the detection of Pe1-Fe3 mRNA was correlated with poor postoperative survival periods in NSCLC, consistent with a previous finding in which FER overexpression was correlated with poor postoperative prognosis in NSCLC. This report is the first to suggest a correlation between chimeric mRNA and the expression level of parental mRNA. Furthermore, our findings may be clinically beneficial, suggesting that PJA2-FER mRNAs might serve as a novel prognostic biomarker in NSCLC.

10.1371/journal.pone.0067876 - Cancer Sci

[1062]

TÍTULO / TITLE: - The role of Cancer-Testis antigens as predictive and prognostic markers in non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e67876. doi: 10.1371/journal.pone.0067876. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0067876](https://doi.org/10.1371/journal.pone.0067876)

AUTORES / AUTHORS: - John T; Starmans MH; Chen YT; Russell PA; Barnett SA; White SC; Mitchell PL; Walkiewicz M; Azad A; Lambin P; Tsao MS; Deb S; Altorki N; Wright G; Knight S; Boutros PC; Cebon JS

INSTITUCIÓN / INSTITUTION: - Ludwig Institute for Cancer Research, Austin Health, Melbourne, Australia. tom.john@ludwig.edu.au

RESUMEN / SUMMARY: - BACKGROUND: Cancer-Testis Antigens (CTAs) are immunogenic proteins that are poor prognostic markers in non-small cell lung cancer (NSCLC). We investigated expression of CTAs in NSCLC and their association with response to

chemotherapy, genetic mutations and survival. METHODS: We studied 199 patients with pathological N2 NSCLC treated with neoadjuvant chemotherapy (NAC; n = 94), post-operative observation (n = 49), adjuvant chemotherapy (n = 47) or unknown (n = 9). Immunohistochemistry for NY-ESO-1, MAGE-A and MAGE-C1 was performed. Clinicopathological features, response to neoadjuvant treatment and overall survival were correlated. DNA mutations were characterized using the Sequenom Oncocarta panel v1.0. Affymetrix data from the JBR.10 adjuvant chemotherapy study were obtained from a public repository, normalised and mapped for CTAs. RESULTS: NY-ESO-1 was expressed in 50/199 (25%) samples. Expression of NY-ESO-1 in the NAC cohort was associated with significantly increased response rates (P = 0.03), but not overall survival. In the post-operative cohort, multivariate analyses identified NY-ESO-1 as an independent poor prognostic marker for those not treated with chemotherapy (HR 2.61, 95% CI 1.28-5.33; P = 0.008), whereas treatment with chemotherapy and expression of NY-ESO-1 was an independent predictor of improved survival (HR 0.267, 95% CI 0.07-0.980; P = 0.046). Similar findings for MAGE-A were seen, but did not meet statistical significance. Independent gene expression data from the JBR.10 dataset support these findings but were underpowered to demonstrate significant differences. There was no association between oncogenic mutations and CTA expression. CONCLUSIONS: NY-ESO-1 was predictive of increased response to neoadjuvant chemotherapy and benefit from adjuvant chemotherapy. Further studies investigating the relationship between these findings and immune mechanisms are warranted.

[1063]

TÍTULO / TITLE: - Progesterone Stimulates Proliferation and Promotes Cytoplasmic Localization of the Cell Cycle Inhibitor p27 in Steroid Receptor Positive Breast Cancers.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Horm Cancer. 2013 Aug 31.

●● Enlace al texto completo (gratis o de pago) [1007/s12672-013-0159-5](#)

AUTORES / AUTHORS: - Kariagina A; Xie J; Langohr IM; Opreanu RC; Basson MD; Haslam SZ

INSTITUCIÓN / INSTITUTION: - Department of Physiology, College of Human Medicine, Michigan State University, East Lansing, MI, USA, kariagin@msu.edu.

RESUMEN / SUMMARY: - Progestins are reported to increase the risk of more aggressive estrogen receptor positive, progesterone receptor positive (ER+ PR+) breast cancers in postmenopausal women. Using an in vivo rat model of ER+ PR+ mammary cancer, we show that tumors arising in the presence of estrogen and progesterone exhibit increased proliferation and decreased nuclear expression of the cell cycle inhibitor p27 compared with tumors growing in the presence of estrogen alone. In human T47D breast cancer cells, progestin increased proliferation and decreased nuclear p27 expression. The decrease of nuclear p27 protein was dependent on activation of Src

and PI3K by progesterone receptor isoforms PRA or PRB. Importantly, increased proliferation and decreased nuclear p27 expression were observed in invasive breast carcinoma compared with carcinoma in situ. These results suggest that progesterone specifically regulates intracellular localization of p27 protein and proliferation. Therefore, progesterone-activated pathways can provide useful therapeutic targets for treatment of more aggressive ER+ PR+ breast cancers.

[1064]

TÍTULO / TITLE: - Synthesis, Structure Activity Relationships and Biological Activity Evaluation of Novel Spirocyclic Thiazolidin-4-ones as Potential Anti-Breast Cancer and Epidermal Growth Factor Receptor Inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Drug Res (Stuttg). 2013 Aug 15.

●● Enlace al texto completo (gratis o de pago) [1055/s-0033-1351314](#)

AUTORES / AUTHORS: - Fleita DH; Sakka OK; Mohareb RM

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, American University in Cairo, New Cairo, Egypt.

RESUMEN / SUMMARY: - A series of triazaspiro[4.5]dec-8-ene benzylidene derivatives containing thiazolidinone ring system (6-18) have been designed, synthesized and their biological activities evaluated as potential epidermal growth factor receptor inhibitors. Among them, 9-amino-2-(4-nitrobenzylidene)-3-oxo-4-phenyl-7-thioxo-1-thia-4,6,8-triazaspiro[4.5]dec-8-ene-10-carbonitrile (18) displayed the most potent inhibitory activity (IC₅₀=6.355 µM). Antiproliferative assay results indicated that compound 18 exhibited moderate antiproliferative activity against MCF-7 cell line in vitro; with GI₅₀ value of 30.6 µM. In addition, compounds 7 and 15 displayed the highest antiproliferative activity at a common GI₅₀ value of 10.8 µM. Docking simulation was performed to determine the probable binding model and to pursuit information regarding the activity of compound 18. Based on the preliminary results, compound 18 could be used as an attractive building block for designing potential epidermal growth factor receptor inhibitors.

[1065]

TÍTULO / TITLE: - Class III beta-tubulin is a predictive marker for taxane-based chemotherapy in recurrent and metastatic gastric cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Sep 23;13(1):431.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-431](#)

AUTORES / AUTHORS: - Hwang JE; Hong JY; Kim K; Kim SH; Choi WY; Kim MJ; Jung SH; Shim HJ; Bae WK; Hwang EC; Lee KH; Lee JH; Cho SH; Chung IJ

RESUMEN / SUMMARY: - BACKGROUND: Class III beta-tubulin (TUBB3) is a prognostic marker in various tumors, but the role of TUBB3 in advanced gastric cancer is not

clearly defined. We analyzed the significance of TUBB3 expression, along with that of excision repair cross-complementation group 1 (ERCC1) in recurrent and metastatic gastric cancer patients receiving taxane-based first-line palliative chemotherapy. METHODS: We reviewed the cases of 146 patients with advanced gastric adenocarcinoma who received taxane-based first-line palliative chemotherapy between 2004 and 2010 at Chonnam National University Hwasun Hospital (Gwangju, Korea). Immunohistochemical staining for TUBB3 and ERCC1 was performed using paraffin wax-embedded tumor tissues. We evaluated the patients' response to chemotherapy, progression-free survival (PFS), and overall survival (OS). RESULTS: In total, 146 patients with advanced gastric cancer received docetaxel and cisplatin (n = 15) or paclitaxel and cisplatin (n = 131). The median PFS was significantly shorter for patients with high-level TUBB3 expression than for patients with low-level TUBB3 expression (3.63 vs. 6.67 months, P = 0.001). OS was not associated with TUBB3 expression (13.1 vs. 13.1 months, P = 0.769). By multivariate analysis, only TUBB3 was related to a shorter PFS (HR 2.74, 95% CI 1.91-3.91, P = 0.001). Patients with high-level ERCC1 expression showed a lower response rate than patients with low-level ERCC1 expression (24 vs. 63.2 %, P = 0.001); however, ERCC1 had no clinical effect on PFS or OS. CONCLUSIONS: TUBB3 was a strong predictive marker in recurrent and metastatic gastric cancer patients receiving taxane-based first-line palliative chemotherapy. No clinical impact of ERCC1 was evident in this setting.

[1066]

TÍTULO / TITLE: - Combination of mTOR and EGFR Kinase Inhibitors Blocks mTORC1 and mTORC2 Kinase Activity and Suppresses the Progression of Colorectal Carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 22;8(8):e73175. doi: 10.1371/journal.pone.0073175.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073175](#)

AUTORES / AUTHORS: - Wang Q; Wei F; Li C; Lv G; Wang G; Liu T; Bellail AC; Hao C

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal Surgery, First Hospital of Jilin University, Changchun, Jilin, China.

RESUMEN / SUMMARY: - Mammalian target of rapamycin complex 1 and 2 (mTORC1/2) are overactive in colorectal carcinomas; however, the first generation of mTOR inhibitors such as rapamycin have failed to show clinical benefits in treating colorectal carcinoma in part due to their effects only on mTORC1. The second generation of mTOR inhibitors such as PP242 targets mTOR kinase; thus, they are capable of inhibiting both mTORC1 and mTORC2. To examine the therapeutic potential of the mTOR kinase inhibitors, we treated a panel of colorectal carcinoma cell lines with PP242. Western blotting showed that the PP242 inhibition of mTORC2-mediated AKT phosphorylation at Ser 473 (AKT(S473)) was transient only in the first few hours of the PP242 treatment. Receptor tyrosine kinase arrays further revealed that PP242

treatment increased the phosphorylated epidermal growth factor receptor (EGFR) at Tyr 1068 (EGFR(T1068)). The parallel increase of AKT(S473) and EGFR(T1068) in the cells following PP242 treatment raised the possibility that EGFR phosphorylation might contribute to the PP242 incomplete inhibition of mTORC2. To test this notion, we showed that the combination of PP242 with erlotinib, an EGFR small molecule inhibitor, blocked both mTORC1 and mTORC2 kinase activity. In addition, we showed that the combination treatment inhibited colony formation, blocked cell growth and induced apoptotic cell death. A systemic administration of PP242 and erlotinib resulted in the progression suppression of colorectal carcinoma xenografts in mice. This study suggests that the combination of mTOR kinase and EGFR inhibitors may provide an effective treatment of colorectal carcinoma.

[1067]

TÍTULO / TITLE: - Cyclic RGD-Linked Polymeric Micelles for Targeted Delivery of Platinum Anticancer Drugs to Glioblastoma through the Blood-Brain Tumor Barrier.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ACS Nano. 2013 Sep 18.

●● Enlace al texto completo (gratis o de pago) [1021/nn402662d](#)

AUTORES / AUTHORS: - Miura Y; Takenaka T; Toh K; Wu S; Nishihara H; Kano MR; Ino Y; Nomoto T; Matsumoto Y; Koyama H; Cabral H; Nishiyama N; Kataoka K

INSTITUCIÓN / INSTITUTION: - Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.

RESUMEN / SUMMARY: - Ligand-mediated drug delivery systems have enormous potential for improving the efficacy of cancer treatment. In particular, Arg-Gly-Asp peptides are promising ligand molecules for targeting $\alpha_3\beta_5$ integrins, which are overexpressed in angiogenic sites and tumors, such as intractable human glioblastoma (U87MG). We here achieved highly efficient drug delivery to U87MG tumors by using a platinum anticancer drug-incorporating polymeric micelle (PM) with cyclic Arg-Gly-Asp (cRGD) ligand molecules. Intravital confocal laser scanning microscopy revealed that the cRGD-linked polymeric micelles (cRGD/m) accumulated rapidly and had high permeability from vessels into the tumor parenchyma compared with the PM having nontargeted ligand, "cyclic-Arg-Ala-Asp" (cRAD). As both cRGD/m- and cRAD-linked polymeric micelles have similar characteristics, including their size, surface charge, and the amount of incorporated drugs, it is likely that the selective and accelerated accumulation of cRGD/m into tumors occurred via an active internalization pathway, possibly transcytosis, thereby producing significant antitumor effects in an orthotopic mouse model of U87MG human glioblastoma.

[1068]

TÍTULO / TITLE: - Harnessing the genome for characterization of G-protein coupled receptors in cancer pathogenesis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - FEBS J. 2013 Oct;280(19):4729-38. doi: 10.1111/febs.12473. Epub 2013 Sep 2.

●● Enlace al texto completo (gratis o de pago) [1111/febs.12473](#)

AUTORES / AUTHORS: - Feigin ME

INSTITUCIÓN / INSTITUTION: - Cold Spring Harbor Laboratory, NY, USA.

RESUMEN / SUMMARY: - G-protein coupled receptors (GPCRs) mediate numerous physiological processes and represent the targets for a vast array of therapeutics for diseases ranging from depression to hypertension to reflux. Despite the recognition that GPCRs can act as oncogenes and tumour suppressors by regulating oncogenic signalling networks, few drugs targeting GPCRs are utilized in cancer therapy. Recent large-scale genome-wide analyses of multiple human tumours have uncovered novel GPCRs altered in cancer. However, work aiming to determine which GPCRs from these lists are the drivers of tumorigenesis, and hence valid therapeutic targets, comprises a formidable challenge. The present review highlights recent studies providing evidence that GPCRs are relevant targets for cancer therapy through their effects on known cancer signalling pathways, tumour progression, invasion and metastasis, and the microenvironment. Furthermore, the review also explores how genomic analysis is beginning to highlight GPCRs as therapeutic targets in the age of personalized medicine.

[1069]

TÍTULO / TITLE: - Novel diagnostic and prognostic biomarkers in biliary tract cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Opin Med Diagn. 2013 Sep;7(5):487-99. doi: 10.1517/17530059.2013.826646.

●● Enlace al texto completo (gratis o de pago) [1517/17530059.2013.826646](#)

AUTORES / AUTHORS: - Skipworth JR; Timms JF; Pereira SP

INSTITUCIÓN / INSTITUTION: - University College London, Division of Surgery and Interventional Science, 4th Floor, 74 Huntley Street, London, WC1E6AU, UK.

RESUMEN / SUMMARY: - Introduction: The worldwide incidence of biliary tract carcinoma (BTC, tumours of the bile ducts and gall-bladder) continues to rise, with the only potentially curative treatment remaining surgical resection or transplantation, possible in only a minority of patients. Late presentation and a paucity of effective treatments mandate the development of techniques for early lesion detection. Areas covered: This article reviews currently available biomarkers for the diagnosis and prognosis of BTC, as well as recently published studies describing novel serum, bile and urinary biomarkers. Expert opinion: The incorporation of novel analysis techniques, such as digital image analysis and fluorescence in situ hybridization, into existing management

algorithms enhances the accuracy of brush cytology taken at the time of therapeutic endoscopy. However, a key goal is the discovery of reliable non-invasive biomarkers with high sensitivity and specificity. Recent advances in gene sequencing and expression, clonal evolution and tumour heterogeneity in other cancers should advance understanding of BTC tumour biology and facilitate biomarker discovery.

[1070]

TÍTULO / TITLE: - Lack of Association of BRAF Mutation With Negative Prognostic Indicators in Papillary Thyroid Carcinoma: The University of California, San Francisco, Experience.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - JAMA. %8?(3k+]3s <http://jama.ama-assn.org/search.dtl> ●●
JAMA: <> Otolaryngol Head Neck Surg. 2013 Sep 12. doi: 10.1001/jamaoto.2013.4501.

●● Enlace al texto completo (gratis o de pago) [1001/jamaoto.2013.4501](http://jamaoto.2013.4501)

AUTORES / AUTHORS: - Gouveia C; Can NT; Bostrom A; Grenert JP; van Zante A; Orloff LA

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, San Francisco2Department of Otolaryngology-Head and Neck Surgery, Northwestern University, Chicago, Illinois.

RESUMEN / SUMMARY: - IMPORTANCE Papillary thyroid carcinoma (PTC) is the most common endocrine neoplasm. B-type raf kinase (BRAF) V600E mutation has been proposed as a negative prognostic indicator in PTC, and patients harboring it should receive more aggressive initial therapy. OBJECTIVE To assess the significance of BRAF V600E mutation in PTC in the largest US sample to date. DESIGN We identified patients from our institution's pathology archives diagnosed as having PTC and meeting criteria for BRAF mutation testing. Medical records were analyzed for BRAF status (positive or negative) and a list of standardized clinicopathologic features. PARTICIPANTS A total of 429 patients with PTC at an academic medical center. MAIN OUTCOMES AND MEASURES Clinicopathologic features in patients with PTC with and without BRAF mutation. RESULTS Of 429 cases with PTC, 314 (73.2%) were positive for the BRAF mutation and 115 (26.8%) tested negative. BRAF mutation was significantly associated with tumor margin positivity (P = .03) and lymph node metastasis (P = .002) on univariate analysis but not on multivariate study. BRAF mutation was a predictor of male sex (odds ratio [OR], 3.2; 95% CI, 1.4-7.2), total thyroidectomy (OR, 2.6; 95% CI, 1.1-6.2), and a negative predictor of follicular variant PTC (OR, 0.1; 95% CI, 0.1-0.4). There was no significant association between BRAF positivity and tumor multicentricity, lymphovascular invasion, extranodal extension, central neck involvement, advanced stage (stage III or IV), and distant metastasis. CONCLUSIONS AND RELEVANCE BRAF V600E mutation has been extensively studied in relation to negative prognostic indicators in PTC, with no consistent relationship emerging. Two recent meta-analyses showed an overall association between BRAF status and aggressive disease features and called for tailoring treatment plans in patients

accordingly. In this, the largest US study to date, BRAF status was not significantly associated with most clinicopathologic features suggestive of more aggressive disease.

[1071]

TÍTULO / TITLE: - Systematic Analyses of the Cytotoxic Effects of Compound 11^a, a Putative Synthetic Agonist of Photoreceptor-Specific Nuclear Receptor (PNR), in Cancer Cell Lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 16;8(9):e75198. doi: 10.1371/journal.pone.0075198.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0075198](https://doi.org/10.1371/journal.pone.0075198)

AUTORES / AUTHORS: - Zhao Z; Wang L; Wen Z; Ayaz-Guner S; Wang Y; Ahlquist P; Xu W

INSTITUCIÓN / INSTITUTION: - McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, Wisconsin, United States of America.

RESUMEN / SUMMARY: - Photoreceptor cell-specific receptor (PNR/NR2E3) is an orphan nuclear receptor that plays a critical role in retinal development and photoreceptor maintenance. The disease-causing mutations in PNR have a pleiotropic effect resulting in varying retinal diseases. Recently, PNR has been implicated in control of cellular functions in cancer cells. PNR was reported to be a novel regulator of ERalpha expression in breast cancer cells, and high PNR expression correlates with favorable response to tamoxifen treatment. Moreover, PNR was shown to increase p53 stability in HeLa cells, implying that PNR may be a therapeutic target in this and other cancers that retain a wild type p53 gene. To facilitate further understanding of PNR functions in cancer, we characterized compound 11^a, a synthetic, putative PNR agonist in several cell-based assays. Interestingly, we showed that 11^a failed to activate PNR and its cytotoxicity was independent of PNR expression, excluding PNR as a mediator for 11^a cytotoxicity. Systematic analyses of the cytotoxic effects of 11^a in NCI-60 cell lines revealed a strong positive correlation of cytotoxicity with p53 status, i.e., p53 wild type cell lines were significantly more sensitive to 11^a than p53 mutated or null cell lines. Furthermore, using HCT116 p53+/+ and p53-/- isogenic cell lines we revealed that the mechanism of 11^a-induced cytotoxicity occurred through G1/S phase cell cycle arrest rather than apoptosis. In conclusion, we observed a correlation of 11^a sensitivity with p53 status but not with PNR expression, suggesting that tumors expressing wild type p53 might be responsive to this compound.

[1072]

TÍTULO / TITLE: - Integrating genomic, epigenomic, and transcriptomic features reveals modular signatures underlying poor prognosis in ovarian cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Rep. 2013 Aug 15;4(3):542-53. doi: 10.1016/j.celrep.2013.07.010. Epub 2013 Aug 8.

●● Enlace al texto completo (gratis o de pago) [1016/j.celrep.2013.07.010](https://doi.org/10.1016/j.celrep.2013.07.010)

AUTORES / AUTHORS: - Zhang W; Liu Y; Sun N; Wang D; Boyd-Kirkup J; Dou X; Han JD

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Computational Biology, Chinese Academy of Sciences-Max Planck Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yue Yang Road, Shanghai 200031, China.

RESUMEN / SUMMARY: - Ovarian cancer has a poor prognosis, with different outcomes for different patients. The mechanism underlying this poor prognosis and heterogeneity is not well understood. We have developed an unbiased, adaptive clustering approach to integratively analyze ovarian cancer genome-wide gene expression, DNA methylation, microRNA expression, and copy number alteration profiles. We uncovered seven previously uncategorized subtypes of ovarian cancer that differ significantly in median survival time. We then developed an algorithm to uncover molecular signatures that distinguish cancer subtypes. Surprisingly, although the good-prognosis subtypes seem to have not been functionally selected, the poor-prognosis ones clearly have been. One subtype has an epithelial-mesenchymal transition signature and a cancer hallmark network, whereas the other two subtypes are enriched for a network centered on SRC and KRAS. Our results suggest molecular signatures that are highly predictive of clinical outcomes and spotlight “driver” genes that could be targeted by subtype-specific treatments.

[1073]

TÍTULO / TITLE: - A 3D QSAR Study of Betulinic Acid Derivatives as Anti-Tumor Agents Using Topomer CoMFA: Model Building Studies and Experimental Verification.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Molecules. 2013 Aug 22;18(9):10228-41. doi: 10.3390/molecules180910228.

●● Enlace al texto completo (gratis o de pago) [3390/molecules180910228](https://doi.org/10.3390/molecules180910228)

AUTORES / AUTHORS: - Ding W; Sun M; Luo S; Xu T; Cao Y; Yan X; Wang Y

INSTITUCIÓN / INSTITUTION: - Alkali Soil Natural Environmental Science Center, Northeast Forestry University/Key Laboratory of Saline-Alkali Vegetation Ecology Restoration in Oil Field, Ministry of Education, Harbin 150040, China. ywang@nefu.edu.cn.

RESUMEN / SUMMARY: - Betulinic acid (BA) is a natural product that exerts its cytotoxicity against various malignant carcinomas without side effects by triggering the mitochondrial pathway to apoptosis. Betulin (BE), the 28-hydroxyl analog of BA, is present in large amounts (up to 30% dry weight) in the outer bark of birch trees, and shares the same pentacyclic triterpenoid core as BA, yet exhibits no significant cytotoxicity. Topomer CoMFA studies were performed on 37 BA and BE derivatives and their in vitro anti-cancer activity results (reported as IC50 values) against HT29 human colon cancer cells in the present study. All derivatives share a common pentacyclic triterpenoid core and the molecules were split into three pieces by cutting at the C-3

and C-28 sites with a consideration toward structural diversity. The analysis gave a leave-one-out cross-validation q^2 value of 0.722 and a non-cross-validation r^2 value of 0.974, which suggested that the model has good predictive ability ($q^2 > 0.2$). The contour maps illustrated that bulky and electron-donating groups would be favorable for activity at the C-28 site, and a moderately bulky and electron-withdrawing group near the C-3 site would improve this activity. BE derivatives were designed and synthesized according to the modeling result, whereby bulky electronegative groups (maleyl, phthalyl, and hexahydrophthalyl groups) were directly introduced at the C-28 position of BE. The in vitro cytotoxicity values of the given analogs against HT29 cells were consistent with the predicted values, proving that the present topomer CoMFA model is successful and that it could potentially guide the synthesis of new betulinic acid derivatives with high anti-cancer activity. The IC₅₀ values of these three new compounds were also assayed in five other tumor cell lines. 28-O-hexahydrophthalyl BE exhibited the greatest anti-cancer activities and its IC₅₀ values were lower than those of BA in all cell lines, excluding DU145 cells.

[1074]

TÍTULO / TITLE: - Interferon Inducible IFI16 Expression in p16 Positive Squamous Cell Carcinoma of the Oropharynx.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ISRN Otolaryngol. 2013;2013:263271. doi: 10.1155/2013/263271.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/263271](#)

AUTORES / AUTHORS: - Yamauchi M; Nakano T; Nakashima T; Yasumatsu R; Hashimoto K; Toh S; Shiratsuchi H; Oda Y; Komune S

INSTITUCIÓN / INSTITUTION: - Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan.

RESUMEN / SUMMARY: - Human-papillomavirus- (HPV-) positive oropharyngeal squamous cell carcinomas (OPSCC) are reported to be more responsive to treatment and to be related to a favorable prognosis compared with non-HPV carcinomas. However, the molecular basis of the responsiveness is unclear. Interferon inducible IFI16, which is implicated in the control of cell growth, apoptosis, angiogenesis, and immunomodulation in various types of cancers, is reported to be frequently expressed in the HPV-positive head and neck SCC and to correlate with a better prognosis. In this study, we hypothesized that HPV related OPSCC expresses IFI16 resulting in favorable prognosis. To clarify the relationship between the prognosis of HPV related OPSCC patients and IFI16 status, we examined immunohistologically the pretreatment specimens of OPSCC for the expression of p16 as a surrogate marker of HPV infection and IFI16. We could not show that the expression of IFI16 is associated with that of p16. There was no significant difference in the survival rate between IFI16 positive and negative groups. Patients with p16 negative tumor exhibited worse survival rate

regardless of IFI16 status. In this limited case series, we could not conclude that IFI16 expression is altered in p16 positive OPSCC and that it would be a new predictive marker or a useful therapeutic tool.

[1075]

TÍTULO / TITLE: - Antrodia camphorata Grown on Germinated Brown Rice Inhibits HT-29 Human Colon Carcinoma Proliferation Through Inducing G0/G1 Phase Arrest and Apoptosis by Targeting the beta-Catenin Signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Med Food. 2013 Aug;16(8):681-91. doi: 10.1089/jmf.2012.2605.

●● Enlace al texto completo (gratis o de pago) [1089/jmf.2012.2605](#)

AUTORES / AUTHORS: - Park DK; Lim YH; Park HJ

INSTITUCIÓN / INSTITUTION: - 1 Cell Activation Research Institute, Konkuk University , Seoul, Korea.

RESUMEN / SUMMARY: - Abstract Antrodia camphorata (AC) has been used as a traditional medicine to treat food and drug intoxication, diarrhea, abdominal pain, hypertension, pruritis (skin itch), and liver cancer in East Asia. In this study, we investigated anticancer activities of AC grown on germinated brown rice (CBR) in HT-29 human colon cancer cells. We found that the inhibitory efficacy of CBR 80% ethanol (EtOH) extract on HT-29 and CT-26 cell proliferation was more effective than ordinary AC EtOH 80% extract. Next, 80% EtOH extract of CBR was further separated into four fractions; hexane, ethyl acetate (EtOAc), butanol (BuOH), and water. Among them, CBR EtOAc fraction showed the strongest inhibitory activity against HT-29 cell proliferation. Therefore, CBR EtOAc fraction was chosen for further studies. Annexin V-fluorescein isothiocyanate staining data indicated that CBR EtOAc fraction induced apoptosis. Induction of G0/G1 cell cycle arrest on human colon carcinoma cell was observed in CBR EtOAc fraction-treated cells. We found that CBR decreased the level of proteins involved in G0/G1 cell cycle arrest and apoptosis. CBR EtOAc fraction inhibited the beta-catenin signaling pathway, supporting its suppressive activity on the level of cyclin D1. High performance liquid chromatography analysis data indicated that CBR EtOAc fraction contained adenosine. This is the first investigation that CBR has a greater potential as a novel chemopreventive agent than AC against colon cancer. These data suggest that CBR might be useful as a chemopreventive agent against colorectal cancer.

[1076]

TÍTULO / TITLE: - Adjuvant chemotherapy after pulmonary resection for lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Thorac Surg Clin. 2013 Aug;23(3):401-10. doi: 10.1016/j.thorsurg.2013.04.005. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1016/j.thorsurg.2013.04.005](#)

AUTORES / AUTHORS: - Mascaux C; Shepherd FA

INSTITUCIÓN / INSTITUTION: - Princess Margaret Cancer Centre, University of Health Network, University of Toronto, Toronto, Ontario, Canada.

RESUMEN / SUMMARY: - Adjuvant chemotherapy using a cisplatin-based regimen is currently recommended for patients with stage II and III non-small cell lung cancer (NSCLC) after complete tumor resection and may be considered for patients with stage IB NSCLC. Although adjuvant chemotherapy after complete resection of localized NSCLC is associated with an absolute survival advantage of approximately 5% at 5 years, there is still a relatively high risk of relapse even for early-stage NSCLC. Efforts are ongoing to identify new treatments in the adjuvant setting and to select patients for individualized treatment based on biomarkers.

[1077]

TÍTULO / TITLE: - Thymoquinone induces mitochondria-mediated apoptosis in acute lymphoblastic leukaemia in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Molecules. 2013 Sep 12;18(9):11219-40. doi: 10.3390/molecules180911219.

●● Enlace al texto completo (gratis o de pago) [3390/molecules180911219](#)

AUTORES / AUTHORS: - Salim LZ; Mohan S; Othman R; Abdelwahab SI; Kamalidehghan B; Sheikh BY; Ibrahim MY

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia. syammohanm@yahoo.com.

RESUMEN / SUMMARY: - There has been a growing interest in naturally occurring compounds from traditional medicine with anti-cancer potential. Nigella sativa (black seed) is one of the most widely studied plants. This annual herb grows in countries bordering the Mediterranean Sea and India. Thymoquinone (TQ) is an active ingredient isolated from Nigella sativa. The anti-cancer effect of TQ, via the induction of apoptosis resulting from mitochondrial dysfunction, was assessed in an acute lymphocyte leukemic cell line (CEMss) with an IC₅₀ of 1.5 microg/mL. A significant increase in chromatin condensation in the cell nucleus was observed using fluorescence analysis. The apoptosis was then confirmed by Annexin V and an increased number of cellular DNA breaks in treated cells were observed as a DNA ladder. Treatment of CEMss cells with TQ encouraged apoptosis with cell death-transducing signals by a down-regulation of Bcl-2 and up-regulation of Bax. Moreover, the significant generation of cellular ROS, HSP70 and activation of caspases 3 and 8 were also observed in the treated cells. The mitochondrial apoptosis was clearly associated with the S phase cell cycle arrest. In conclusion, the results from the current study indicated that TQ could be a promising agent for the treatment of leukemia.

[1078]

TÍTULO / TITLE: - Cucurbitacin E as Inducer of Cell Death and Apoptosis in Human Oral Squamous Cell Carcinoma Cell Line SAS.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Aug 20;14(8):17147-56. doi: 10.3390/ijms140817147.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140817147](#)

AUTORES / AUTHORS: - Hung CM; Chang CC; Lin CW; Ko SY; Hsu YC

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, E-Da Hospital, I-Shou University, Kaohsiung 82445, Taiwan. ed100647@edah.org.tw.

RESUMEN / SUMMARY: - Human oral squamous cell carcinoma (OSCC) is a common form of malignant cancer, for which radiotherapy or chemotherapy are the main treatment methods. Cucurbitacin E (CuE) is a natural compound previously shown to be an antifeedant as well as a potent chemopreventive agent against several types of cancer. The present study investigates anti-proliferation (using MTT assay, CuE demonstrated cytotoxic activity against SAS cell with IC50 values at 3.69 micromM) and induced apoptosis of human oral squamous cell carcinoma SAS cells after 24 h treatment with CuE. Mitochondrial membrane potential (MMP) and caspase activity were studied and our results indicate that CuE inhibits cell proliferation as well as the activation of apoptosis in SAS cells. Both effects increased in proportion to the dosage of CuE and apoptosis was induced via mitochondria- and caspase-dependent pathways. CuE can induce cell death by a mechanism that is not dependent on apoptosis induction, and thus represents a promising anticancer agent for prevention and treatment of OSCC.

[1079]

TÍTULO / TITLE: - Proteomics study of open biopsy samples identifies peroxiredoxin 2 as a predictive biomarker of response to induction chemotherapy in osteosarcoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Proteomics. 2013 Aug 2;91C:393-404. doi: 10.1016/j.jprot.2013.07.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.jprot.2013.07.022](#)

AUTORES / AUTHORS: - Kubota D; Mukaiharu K; Yoshida A; Tsuda H; Kawai A; Kondo T

INSTITUCIÓN / INSTITUTION: - Division of Pharmacoproteomics, National Cancer Center Research Institute, Tokyo, Japan; Department of Orthopedic Surgery, Juntendo University School of Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - We attempted to identify biomarkers that would predict responsiveness of osteosarcoma (OS) to induction chemotherapy. Tumor tissues obtained by open biopsy before induction chemotherapy were investigated. On the basis of histological observations at the time of surgery and the Huvos grading system, 7 patients were classified as good responders and the other 6 as poor responders. Protein expression profiling was performed by two-dimensional difference gel

electrophoresis. Among 3494 protein spots observed, the intensity of 33 spots was found to differ significantly between the two patient groups. The proteins for these 33 protein spots were identified by mass spectrometry. The higher expression of peroxiredoxin 2 (PRDX2) in poor responders was confirmed by Western blotting. Gene silencing assay demonstrated that reduced expression of PRDX2 was associated with increased sensitivity of OS cells to chemotherapeutic drugs such as methotrexate, doxorubicin and cisplatin. Moreover, siRNA-induced silencing of PRDX2 resulted in a decrease of cell proliferation, invasion and migration. These findings indicated that PRDX2 would be a candidate biomarker of response to induction chemotherapy. Measurement of PRDX2 in open biopsy samples before treatment may contribute to risk stratification therapy for OS. **BIOLOGICAL SIGNIFICANCE:** The response of osteosarcoma patients to induction chemotherapy is critical because the prognosis of responders is quite favorable, whereas that of non-responders is poor. Although there are many therapeutic options for osteosarcoma, no parameter for predicting the response to induction chemotherapy has been available. We conducted a proteomics study aimed at developing a biomarker that would predict the response of osteosarcoma to induction chemotherapy. Using open biopsy samples obtained before chemotherapy, we conducted 2D-DIGE with our originally devised large-format electrophoresis apparatus and identified peroxiredoxin 2 (PRDX2) as a novel predictive biomarker. The diagnostic performance of PRDX2 was confirmed by ROC analysis, and its functional properties were investigated in a series of in vitro functional assays. Our findings indicate the possible application of PRDX2 as a predictive biomarker in patients with osteosarcoma.

[1080]

TÍTULO / TITLE: - Sinulariolide Induced Hepatocellular Carcinoma Apoptosis through Activation of Mitochondrial-Related Apoptotic and PERK/eIF2alpha/ATF4/CHOP Pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Molecules. 2013 Aug 22;18(9):10146-61. doi: 10.3390/molecules180910146.

●● Enlace al texto completo (gratis o de pago) [3390/molecules180910146](#)

AUTORES / AUTHORS: - Chen YJ; Su JH; Tsao CY; Hung CT; Chao HH; Lin JJ; Liao MH; Yang ZY; Huang HH; Tsai FJ; Weng SH; Wu YJ

INSTITUCIÓN / INSTITUTION: - Department of Physical Medicine and Rehabilitation, Kaohsiung Medical University Hospital, Kaohsiung 80761, Taiwan.
wyr924@ms24.hinet.net.

RESUMEN / SUMMARY: - Sinulariolide, an active compound isolated from the cultured soft coral *Sinularia flexibilis*, has potent anti-microbial and anti-tumorigenesis effects towards melanoma and bladder cancer cells. In this study, we investigated the effects of sinulariolide on hepatocellular carcinoma (HCC) cell growth and protein expression.

Sinulariolide suppressed the proliferation and colony formation of HCC HA22T cells in a dose-dependent manner and induced both early and late apoptosis according to flow cytometry, Annexin V/PI stain and TUNEL/DAPI stain analyses. A mechanistic analysis demonstrated that sinulariolide-induced apoptosis was activated through a mitochondria-related pathway, showing up-regulation of Bax, Bad and AIF, and down-regulation of Bcl-2, Bcl-xL, Mcl-1 and p-Bad. Sinulariolide treatment led to loss of the mitochondrial membrane potential, release of mitochondrial cytochrome c to the cytosol, and activation of both caspase-9 and caspase-3. Sinulariolide-induced apoptosis was significantly blocked by the caspase inhibitors Z-VAD-FMK and Z-DEVD-FMK. The increased expression of cleaved PARP also suggested that caspase-independent apoptotic pathway was involved. In the western blotting; the elevation of ER chaperones GRP78; GRP94; and CALR; as well as up-regulations of PERK/eIF2alpha/ATF4/CHOP; and diminished cell death with pre-treatment of eIF2alpha phosphatase inhibitor; salubrinal; implicated the involvement of ER stress-mediated PERK/eIF2alpha/ATF4/CHOP apoptotic pathway following sinulariolide treatment in hepatoma cells. The current study suggested sinulariolide-induced hepatoma cell cytotoxicity involved multiple apoptotic signal pathways. This may implicate that sinulariolide is a potential compound for the treatment of hepatocellular carcinoma.

[1081]

TÍTULO / TITLE: - MiR-429 up-regulation induces apoptosis and suppresses invasion by targeting Bcl-2 and SP-1 in esophageal carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Oncol (Dordr). 2013 Oct;36(5):385-94. doi: 10.1007/s13402-013-0144-6. Epub 2013 Sep 3.

●● Enlace al texto completo (gratis o de pago) [1007/s13402-013-0144-6](#)

AUTORES / AUTHORS: - Wang Y; Li M; Zang W; Ma Y; Wang N; Li P; Wang T; Zhao G

INSTITUCIÓN / INSTITUTION: - Department of Microbiology and Immunology, College of Basic Medical Sciences, Zhengzhou University, Zhengzhou, 450001, Henan Province, China.

RESUMEN / SUMMARY: - PURPOSE: MicroRNAs (miRNAs) may act as oncogenes or tumor suppressor genes and, as such, they may play a role in cancer development. We investigated miR-429 expression levels in a cohort of esophageal carcinomas (EC) to assess its impact on EC cell growth, apoptosis and invasion. METHODS: qRT-PCR assays were used to quantify miR-429 expression levels in 32 paired EC samples and adjacent non-neoplastic tissues. Assays for cell growth, apoptosis, caspase activity and trans-well invasion were used to evaluate the effects of miR-429 expression on EC cells. Luciferase reporter and Western blotting assays were used to test whether the Bcl-2 and specificity protein 1 (SP1) mRNAs serve as major targets of miR-429. RESULTS: The expression levels of miR-429 in EC tissues were found to be lower than those in

adjacent non-neoplastic tissues ($P < 0.05$). This relatively low expression was found to be significantly associated with the occurrence of lymph node metastases ($P < 0.05$). Apoptosis and migration rates were found to be significantly higher in two EC-derived cell lines (EC9706 and KYSE30) transfected with a miR-429 agomir ($P < 0.05$). Subsequent Western blotting and luciferase reporter assays showed that miR-429 can bind to putative binding sites within the Bcl-2 and SP1 mRNA 3' untranslated regions (UTRs) to reduce their expression. CONCLUSIONS: In primary EC tissues miR-429 is expressed at low levels. Up-regulation of miR-429 inhibits invasion and promotes apoptosis in EC cells by targeting Bcl-2 and SP1. Our findings suggest that Bcl-2 and SP1 may serve as major targets of miR-429. This study paves the way for a better understanding of the mechanism underlying EC pathogenesis and the development of novel, targeted therapies.

[1082]

TÍTULO / TITLE: - Erythrophagocytosis Enhances Heme-Dependent Cytotoxicity of Antimalarial Drugs in Canine Histiocytic Sarcoma Cell Line DH82.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Vet Med Sci. 2013 Sep 20.

AUTORES / AUTHORS: - Chikazawa S; Kitahara Y; Ando E; Hori Y; Hoshi F; Kanai K; Ito N; Higuchi S

INSTITUCIÓN / INSTITUTION: - Department of Small Animal Internal Medicine, School of Veterinary Medicine, Kitasato University.

RESUMEN / SUMMARY: - Antimalarial drugs, dihydroartemisinin (DHA) and artesunate (ATS), exhibit iron-dependent cytotoxicity in tumor cells. We hypothesized that erythrophagocytic uptake of heme-iron enhances the cytotoxicity of DHA and ATS. Erythrophagocytic (EP) treatment of the canine histiocytic sarcoma cell line DH82 markedly increased the cytotoxicity of DHA and ATS compared to controls. Succinyl acetone, an inhibitor of intracellular heme synthesis, decreased the cytotoxicity of DHA and ATS in normal cells, but this change was not observed in EP cells. These results suggest that exogenous heme derived from erythrocytes can enhance the cytotoxicity of DHA and ATS. Furthermore, our study suggests that heme could be a novel component of tumor treatment in veterinary medicine.

[1083]

TÍTULO / TITLE: - Tumor delivery efficiency and apoptosis enhancement by EVO nanoparticles on murine hepatic carcinoma cell line H22.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biomed Nanotechnol. 2013 Aug;9(8):1354-61.

AUTORES / AUTHORS: - Zhang Q; Liu Q; Shen J; Chen H; Liu B

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Nanjing Drum Tower Hospital, Nanjing University of Traditional Chinese Medicine, Nanjing 210008, Jiangsu, China.

RESUMEN / SUMMARY: - Nanoscale particles, as drug carriers, have a potential to improve drug therapeutic efficiency. However, the feasible design of the nanostructure containing chemotherapeutic agents and the behavior of the delivery to tumor tissues and cells has not been adequately investigated. In this study, we developed a novel nanoparticle, consisting of a gelatinase-cleavage peptide with poly(ethylene glycol) (PEG) and poly(epsilon-caprolactone) (PCL)-based structure for tumor-targeted EVO (an alkaloid isolated from *Evodia rutaecarpa*) delivery. We found that EVO-NPs were transformed by gelatinases, which could significantly promote drug release and enhance the cellular uptake of EVO ($P < 0.01$). In vivo biodistribution study demonstrated that targeted EVO-NPs could accumulate and remain in the tumor regions. Moreover, EVO-NPs exhibited higher tumor growth suppression than EVO on hepatic H22 tumor model via intravenous administration ($P < 0.01$). Both in vitro and in vivo experiments suggested that the gelatinase-mediated nanoscale delivery system was promising for improvement of antitumor efficacy in various over-expressed gelatinase cancers.

[1084]

TÍTULO / TITLE: - Value of epithelioid morphology and PDGFRA immunostaining pattern for prediction of PDGFRA mutated genotype in gastrointestinal stromal tumors (GISTs).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Clin Exp Pathol. 2013 Aug 15;6(9):1839-46.

AUTORES / AUTHORS: - Agaimy A; Otto C; Braun A; Geddert H; Schaefer IM; Haller F

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Friedrich Alexander University Erlangen, Germany.

RESUMEN / SUMMARY: - AIMS: Genotyping is a prerequisite for tyrosine kinase inhibitor therapy in high risk and malignant GIST. About 10% of GISTs are wild-type for KIT but carry PDGFRA mutations. Applying the traditional approach, mutation analysis of these cases is associated with higher costs if all hotspots regions in KIT (exon 9, 11, 13, 17) are performed at first. Our aim was to evaluate the predictive value of a combined histomorphological-immunohistochemical pattern analysis of PDGFRA-mutated GISTs to efficiently direct KIT and PDGFRA mutation analysis. METHODS: The histomorphology and PDGFRA immunostaining pattern was studied in a test cohort of 26 PDGFRA mutants. This was then validated on a cohort of 94 surgically resected GISTs with mutations in KIT (n=72), PDGFRA (n=15) or with wild-type status (n=7) on a tissue microarray. The histological subtype (spindled, epithelioid, mixed), PDGFRA staining pattern (paranuclear dot-like/Golgi, cytoplasmic and/or membranous), and extent of staining were determined without knowledge of the genotype. The combination of histomorphology and immunophenotype were used to classify tumors

either as PDGFRA- or non-PDGFRA phenotype. RESULTS: PDGFRA-mutated GISTs were significantly more often epithelioid ($p < 0.001$) and had a higher PDGFRA expression, compared to KIT-mutants ($p < 0.001$). Paranuclear PDGFRA immunostaining was almost exclusively observed in PDGFRA mutants ($p < 0.001$). The sensitivity and specificity of this combined histological-immunohistochemical approach to predict the PDGFRA-genotype was 100% and 99%, respectively ($p = 6 \times 10^{-16}$). CONCLUSION: A combination of histomorphology and PDGFRA immunostaining is a reliable predictor of PDGFRA genotype in GIST. This approach allows direct selection of the “gene/exons of relevance” to be analyzed and may help to reduce costs and work load and shorten processing time of GIST genotyping by mutation analysis.

[1085]

TÍTULO / TITLE: - B19, a Novel Monocarbonyl Analogue of Curcumin, Induces Human Ovarian Cancer Cell Apoptosis via Activation of Endoplasmic Reticulum Stress and the Autophagy Signaling Pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Biol Sci. 2013 Aug 14;9(8):766-77. doi: 10.7150/ijbs.5711.

●● [Enlace al texto completo \(gratis o de pago\) 7150/ijbs.5711](#)

AUTORES / AUTHORS: - Qu W; Xiao J; Zhang H; Chen Q; Wang Z; Shi H; Gong L; Chen J; Liu Y; Cao R; Lv J

INSTITUCIÓN / INSTITUTION: - 1. Department of Gynecology and Obstetrics, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, China;

RESUMEN / SUMMARY: - Background: The unfolded protein response, autophagy and endoplasmic reticulum (ER) stress-induced apoptosis regulate tumor cell fate and have become novel signaling targets for the development of cancer therapeutic drugs. Curcumin has been used to treat several different cancers, including ovarian cancer, in clinical trials and research; however, the role of ER stress and autophagy in the therapeutic effects of curcumin and new curcumin analogues remains unclear. Methods: Cell viability was determined using the MTT assay. Apoptosis was detected using flow cytometry with PI/Annexin V-FITC staining. The expression levels of ER stress- and autophagy-related proteins were analyzed by western blotting. The activation of autophagy was detected using immunofluorescence staining. Results: We demonstrated that B19 induced HO8910 cell apoptosis in a dose-responsive manner. We also determined and that this effect was associated with corresponding increases in a series of key components in the UPR and ER stress-mediated apoptosis pathways, followed by caspase 3 cleavage and activation. We also observed that B19 treatment induced autophagy in HO8910 cells. The inhibition of autophagy using 3-methyladenine (3-MA) increased levels of intracellular misfolded proteins, which enhanced ovarian cancer apoptosis. Conclusions: Our data indicate that ER stress and autophagy may play a role in the apoptosis that is induced by the curcumin analogue

B19 in an epithelial ovarian cancer cell line and that autophagy inhibition can increase curcumin analogue-induced apoptosis by inducing severe ER stress.

[1086]

TÍTULO / TITLE: - Dasatinib Inhibits DNA Repair after Radiotherapy Specifically in pSFK-Expressing Tumor Areas in Head and Neck Xenograft Tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Transl Oncol. 2013 Aug 1;6(4):413-9. Print 2013 Aug.

AUTORES / AUTHORS: - Stegeman H; Span PN; Rijken PF; Cockx SC; Wheeler DL; Iida M; van der Kogel AJ; Kaanders JH; Bussink J

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

RESUMEN / SUMMARY: - Src family kinases (SFKs) have been implicated in resistance to both radiation and epidermal growth factor receptor (EGFR) inhibition. Therefore, we investigated whether inhibition of SFK through dasatinib (DSB) can enhance the effect of radiotherapy in two in vivo human head and neck squamous cell carcinoma (HNSCC) models. Response to DSB and/or radiotherapy was assessed with tumor growth delay assays in two HNSCC xenograft models, SCCNij153 and SCCNij202. Effects on EGFR signaling were evaluated with Western blot analysis, and effects on DNA repair, hypoxia, and proliferation were investigated with immunohistochemistry. DSB and radiotherapy induced a significant growth delay in both HNSCC xenograft models, although to a lesser extent in SCCNij202. DSB did not inhibit phosphorylated protein kinase B (pAKT) or phosphorylated extracellular signal-regulated kinase 1/2 (pERK1/2) but did inhibit (phosphorylated) DNA-dependent protein kinase. Moreover, DSB reduced repair of radiation-induced DNA double-strand breaks as shown by an increase of p53-binding protein 1 (53BP1) staining 24 hours after radiation. This effect on DNA repair was only observed in the cell compartment where phosphorylated SFK (pSFK) was expressed: for SCCNij153 tumors in both normoxic and hypoxic areas and for SCCNij202 tumors only in hypoxic areas. No consistent effects of DSB on hypoxia or proliferation were observed. In conclusion, DSB enhances the effect of radiotherapy in vivo by inhibition of radiation-induced DNA repair and is a promising way to improve outcome in HNSCC patients.

[1087]

TÍTULO / TITLE: - Bladder cancer cell-derived exosomes inhibit tumor cell apoptosis and induce cell proliferation in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Oct;8(4):1272-8. doi: 10.3892/mmr.2013.1634. Epub 2013 Aug 14.

●● [Enlace al texto completo \(gratis o de pago\) 3892/mmr.2013.1634](#)

AUTORES / AUTHORS: - Yang L; Wu XH; Wang D; Luo CL; Chen LX

INSTITUCIÓN / INSTITUTION: - Department of Urology, The First Affiliated Hospital of Chongqing Medical University, Yuzhong, Chongqing 400016, P.R. China.

RESUMEN / SUMMARY: - Exosomes are small membrane vesicles released by a variety of mammalian cells into the extracellular space and are involved in cell-to-cell signaling. This study aimed to investigate the effects of bladder cancer cell-derived exosomes on the regulation of tumor cell viability and apoptosis, as well as the underlying molecular events. Exosomes were purified from the supernatants of human bladder cancer T24 cell cultures. Transmission electron microscopy was used to confirm their morphology and western blot analyses determined the protein content of cells. Subsequently, bladder cancer cell lines were treated with different concentrations of exosomes. Tumor cell viability was shown to be reduced, as detected by the Cell Counting Kit-8 assay. Annexin V/flow cytometric assays showed that exosomes inhibited apoptosis of bladder cancer cell lines in a dose- and time-dependent manner. Exosomes were demonstrated to upregulate the expression of Bcl2 and Cyclin D1 proteins, but reduce the levels of Bax and caspase-3 proteins in these cells. Moreover, exosomes dose-dependently increased the expression of phosphorylated Akt and extracellular signal-regulated protein kinase (ERK). In conclusion, this study demonstrated that bladder cancer cell-derived exosomes inhibited tumor cell apoptosis, which was associated with the activation of Akt and ERK pathway genes, suggesting that tumor-derived exosomes are involved in bladder cancer progression. Inhibition of exosome formation and release may therefore be a novel strategy in future treatment of bladder cancer.

[1088]

TÍTULO / TITLE: - Biomarkers and prognostic factors for mesothelioma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Ann Cardiothorac Surg. 2012 Nov;1(4):449-56. doi: 10.3978/j.issn.2225-319X.2012.10.04.

●● [Enlace al texto completo \(gratis o de pago\) 3978/j.issn.2225-319X.2012.10.04](#)

AUTORES / AUTHORS: - Pass HI

INSTITUCIÓN / INSTITUTION: - Stephen E. Banner Professor of Thoracic Oncology, Vice-Chair Research, Department of Cardiothoracic Surgery, Division Chief, General Thoracic Surgery, NYU Langone Medical Center, New York, NY 10016, USA.

[1089]

TÍTULO / TITLE: - Overexpression of nuclear beta-catenin at invasive front in rectal carcinoma is associated with lymph node metastasis and poor prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Transl Oncol. 2013 Sep 17.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12094-013-1108-z](#)

AUTORES / AUTHORS: - Wang L; Zhang X; Li Z; Chai J; Zhang G; Yu Z; Cheng Y; Hu S

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Qilu Hospital, Shandong University, 107 Wenhua Xi Road, Jinan, 250012, Shandong, People's Republic of China, 33943219@qq.com.

RESUMEN / SUMMARY: - BACKGROUND: This study aims to investigate whether nuclear beta-catenin overexpression at invasive front in rectal carcinoma is associated with lymph node metastasis and prognosis. METHODS: Immunohistochemistry was adopted to detect the expression of beta-catenin in rectal carcinoma and lymph node metastatic lesions. Spearman's rank correlation analysis and Tukey's test were used to evaluate the association between nuclear beta-catenin expression at invasive front in rectal carcinoma and lymph node metastasis. Kaplan-Meier method and multivariate Cox regression model were used to evaluate the prognostic value of nuclear beta-catenin overexpression at invasive front in rectal carcinoma for disease-free survival (DFS) and overall survival (OS). RESULTS: Overexpression of nuclear beta-catenin at the invasive front in rectal carcinoma in stage III-N2 was significantly higher than that in stage III-N1 (73.4 vs. 40.4 %, $P < 0.001$). Nuclear beta-catenin expression at the invasive front in rectal carcinoma was associated with the expression of nuclear beta-catenin in corresponding lymph node metastatic lesions ($r = 0.297$, $P < 0.001$). Overexpression of nuclear beta-catenin at the invasive front in rectal carcinoma was correlated with the number of metastatic lymph nodes ($P < 0.001$). Patients with nuclear beta-catenin overexpression at the invasive front in rectal carcinoma had poor DFS ($P = 0.002$) and OS ($P = 0.003$). Moreover, overexpression of nuclear beta-catenin at the invasive front was an independent prognosticator for unfavorable DFS and OS ($P = 0.002$ and 0.001). CONCLUSIONS: Our findings suggest that overexpression of nuclear beta-catenin at the invasive front in rectal carcinoma may be a useful marker to evaluate lymph node metastasis, as well as a promising predictor of poor prognosis.

[1090]

TÍTULO / TITLE: - Complexin-2 (CPLX2) as a potential prognostic biomarker in human lung high grade neuroendocrine tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biomark. 2013;13(3):171-80. doi: 10.3233/CBM-130336.

●● [Enlace al texto completo \(gratis o de pago\) 3233/CBM-130336](#)

AUTORES / AUTHORS: - Komatsu H; Kakehashi A; Nishiyama N; Izumi N; Mizuguchi S; Yamano S; Inoue H; Hanada S; Chung K; Wei M; Suehiro S; Wanibuchi H

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Osaka City University Graduate School of Medicine, Asahi-machi, Abeno-ku, Osaka, Japan.

RESUMEN / SUMMARY: - The present study aimed to identify novel useful clinical biomarker of high grade lung neuroendocrine tumors (LNETs). Based on the results of QSTAR LC-MS/MS analysis, we selected complexin-2 (CPLX2) (upregulated 8.7-fold) as a potential biomarker in high grade human LNETs, and validated its expression

immunohistochemically in comparison with non-small cell lung carcinomas (NSCLCs). CPLX2 was strongly positive in 16.3% of examined LNETs, but completely negative in all adjacent non-cancerous tissues and NSCLCs. Importantly, positive CPLX2 expression was associated with lymph vessel invasion ($P=0.016$), pathological stage ($P=0.031$), and poor disease-specific survival ($P=0.004$) of patients with LNETs. Preoperative serum CPLX2 level measured by ELISA was significantly elevated in high grade LNETs as compared with %NCs non-cancer controls (NCs) ($P=0.002$) and NSCLCs ($P< 0.001$). Receiver operating characteristic (ROC) curve analysis was used for separating high-grade LNET patients from NSCLC patients. The area under the ROC curve (AUC) was 0.825. The calculated optimal cut-off point for CPLX2 level in the serum was 17.8 pg/ml (Youden index=0.591), while sensitivity and specificity was 94.1% and 65.0%, respectively. CPLX2 is suggested as a novel potential clinically useful biomarker for the diagnosis, prognosis and adequate choice of therapy for patients with high grade LNETs.

[1091]

TÍTULO / TITLE: - snoRNPs Regulate Telomerase Activity in Neuroblastoma and Are Associated with Poor Prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Transl Oncol. 2013 Aug 1;6(4):447-57. Print 2013 Aug.

AUTORES / AUTHORS: - von Stedingk K; Koster J; Piqueras M; Noguera R; Navarro S; Pahlman S; Versteeg R; Ora I; Gisselsson D; Lindgren D; Axelson H

INSTITUCIÓN / INSTITUTION: - Center for Molecular Pathology, Department of Laboratory Medicine, Lund University, Skane University Hospital, Malmo, Sweden.

RESUMEN / SUMMARY: - Amplification of the MYCN oncogene is strongly associated with poor prognosis in neuroblastoma (NB). In addition to MYCN amplification, many studies have focused on identifying patients with a poor prognosis based on gene expression profiling. The majority of prognostic signatures today are comprised of large gene lists limiting their clinical application. In addition, although of prognostic significance, most of these signatures fail to identify cellular processes that can explain their relation to prognosis. Here, we determined prognostically predictive genes in a data set containing 251 NBs. Gene Ontology analysis was performed on significant genes with a positive hazard ratio to search for cellular processes associated with poor prognosis. An enrichment in ribonucleoproteins (RNPs) was found. Genes involved in the stabilization and formation of the central small nucleolar RNP (snoRNP) complex were scrutinized using a backward conditional Cox regression resulting in an snoRNP signature consisting of three genes: DKC1, NHP2, and GAR1. The snoRNP signature significantly and independently predicted prognosis when compared to the established clinical risk factors. Association of snoRNP protein expression and prognosis was confirmed using tissue micro-arrays. Knockdown of snoRNP expression in NB cell lines resulted in reduced telomerase activity and an increase in anaphase bridge frequency.

In addition, in patient material, expression of the snoRNP complex was significantly associated with telomerase activity, occurrence of segmental aberrations, and expression-based measurements of chromosomal instability. Together, these results underscore the prognostic value of snoRNP complex expression in NB and suggest a role for snoRNPs in telomere maintenance and genomic stability.

[1092]

TÍTULO / TITLE: - Prognostic implication of neuropilin-1 upregulation in human nasopharyngeal carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Diagn Pathol. 2013 Sep 20;8(1):155.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1746-1596-8-155](#)

AUTORES / AUTHORS: - Xu Y; Li P; Zhang X; Wang J; Gu D; Wang Y

RESUMEN / SUMMARY: - OBJECTIVE: As a receptor for both vascular endothelial growth factors and semaphorin, neuropilin-1 (NRP-1) is reported to be up-regulated in cells of several cancers. However, its roles in human nasopharyngeal carcinoma (NPC) are still unclear. Therefore, the goal of this study was to investigate the expression pattern of NRP-1 in NPC tissues, to clarify the clinical significance of NRP-1 expression in NPC as well as the potential prognostic implication of NRP-1 expression. METHODS: Immunohistochemistry was performed to detect the expression of NRP-1 in tumor tissue samples from 266 NPC patients. The association of NRP-1 protein expression with the clinicopathological characteristics and the prognosis of NPC were subsequently assessed. RESULTS: Immunohistochemical analysis showed that 176 of 266 (66.17%) paraffin-embedded archival NPC biopsies showed high expression of NRP-1, but no non-cancerous nasopharyngeal specimens showed positive expression of NRP-1. In addition, high NRP-1 expression was significantly associated with advanced clinical stage ($P = 0.02$), positive recurrence ($P = 0.001$) and metastasis status ($P = 0.001$) of NPC. Moreover, the NPC patients with higher NRP-1 expression had shorter overall survival, whereas patients with lower NRP-1 expression had better survival ($P < 0.001$). Furthermore, the multivariate analysis indicated that the overexpression of NRP-1 protein was an independent prognostic factor for overall survival ($P = 0.001$) in NPC patients. CONCLUSION: These findings suggest for the first time that NRP-1 upregulation may be a novel biomarker for the prediction of advanced tumor progression and unfavorable prognosis in NPC patients who may benefit from alternative treatment strategy and targeted treatment. Virtual slides: The virtual slides for this article can be found here:

diagnosticpathology.diagnomx.eu/vs/1507827881105018.

[1093]

TÍTULO / TITLE: - c-MET overexpression as a prognostic biomarker in colorectal adenocarcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Gulf J Oncolog. 2013 Jul;1(14):28-34.

AUTORES / AUTHORS: - Abou-Bakr AA; Elbasmi A

INSTITUCIÓN / INSTITUTION: - Dr. Amany A. Abou-Bakr, Associate Professor, Department of Pathology, National Cancer Institute, Cairo University, Egypt. Email:

amany_aboubakr@hotmail.com Tel. +965-66267300.

RESUMEN / SUMMARY: - Background: There is a need for informative molecular markers that provide prognostic information over and above that given by conventional pathologic parameters. This study examined the expression and potential prognostic value of c-MET in colorectal adenocarcinoma. Material and Methods: Two-hundred and thirty cases were evaluable after tissue microarray construction and evaluated for c-MET expression by immunohistochemistry. The results were correlated with standard clinicopathologic prognostic factors. Cases were followed up for 5 years. Results: c-MET was highly expressed in 138 of 230 cases (60%). In normal tissues a negative or weak reaction was observed. Significantly higher c-MET expression was found in the metastatic group (p=0.04). No significant association was found in relation to age, sex, tumor site, tumor size, histological type, or tumor grade (p > 0.05). The 5-year disease free survival for patients with low levels of expression was significantly higher than that for patients with high levels (64% versus 45%, p=0.04). Conclusion: c-MET seems to be a valuable biomarker in colorectal adenocarcinoma; overexpression is a useful prognostic indicator for metastasis and patient outcome. Keywords: c-MET, prognosis, colorectal adenocarcinoma, tissue microarray.

[1094]

TÍTULO / TITLE: - Mycoplasma fermentans Inhibits the Activity of Cellular DNA Topoisomerase I by Activation of PARP1 and Alters the Efficacy of Its Anti-Cancer Inhibitor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 27;8(8):e72377. doi: 10.1371/journal.pone.0072377.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072377](https://doi.org/10.1371/journal.pone.0072377)

AUTORES / AUTHORS: - Afriat R; Horowitz S; Priel E

INSTITUCIÓN / INSTITUTION: - The Shraga Segal Department of Microbiology, Immunology & Genetics, Faculty of Health Sciences, and the Soroka University Medical Center, Ben-Gurion University, Beer-Sheva, Israel.

RESUMEN / SUMMARY: - To understand the effects of the interaction between Mycoplasma and cells on the host cellular function, it is important to elucidate the influences of infection of cells with Mycoplasma on nuclear enzymes such as DNA Topoisomerase type I (Topo I). Human Topo I participates in DNA transaction processes and is the target of anti-cancer drugs, the camptothecins (CPTs). Here we investigated the mechanism by which infection of human tumor cells with Mycoplasma

fermentans affects the activity and expression of cellular Topo I, and the anti-cancer efficacy of CPT. Human cancer cells were infected or treated with live or sonicated *M. fermentans* and the activity and expression of Topo I was determined. *M. fermentans* significantly reduced (by 80%) Topo I activity in the infected/treated tumor cells without affecting the level of Topo I protein. We demonstrate that this reduction in enzyme activity resulted from ADP-ribosylation of the Topo I protein by Poly-ADP-ribose polymerase (PARP-1). In addition, pERK was activated as a result of the induction of the MAPK signal transduction pathway by *M. fermentans*. Since PARP-1 was shown to be activated by pERK, we concluded that *M. fermentans* modified the cellular Topo I activity by activation of PARP-1 via the induction of the MAPK signal transduction pathway. Moreover, the infection of tumor cells with *M. fermentans* diminished the inhibitory effect of CPT. The results of this study suggest that modification of Topo I activity by *M. fermentans* may alter cellular gene expression and the response of tumor cells to Topo I inhibitors, influencing the anti-cancer capacity of Topo I antagonists.

[1095]

TÍTULO / TITLE: - Biological Effects of the Pim Kinase Inhibitor, SGI-1776, in Multiple Myeloma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Aug 26. pii: S2152-2650(13)00236-X. doi: 10.1016/j.clml.2013.05.019.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.05.019

AUTORES / AUTHORS: - Cervantes-Gomez F; Chen LS; Orłowski RZ; Gandhi V

INSTITUCIÓN / INSTITUTION: - Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

RESUMEN / SUMMARY: - BACKGROUND: Pim kinases are constitutively active serine/threonine/tyrosine kinases that are overexpressed in hematological malignancies such as multiple myeloma. Pim kinase substrates are involved in transcription, protein translation, cell proliferation, and apoptosis. SGI-1776 is a potent Pim kinase inhibitor that has proven to be cytotoxic to leukemia and lymphoma cells. Based on this background, we hypothesized that SGI-1776 treatment would result in myeloma cytotoxicity. MATERIALS AND METHODS: To test this, myeloma cell lines and primary CD138+ cells from myeloma patients were treated with SGI-1776 in a dose- and time-dependent manner, and effect on cell death and proliferation, induction of autophagy, and changes in cell cycle profile were measured. RESULTS: SGI-1776 treatment resulted in limited apoptosis in cell lines (mean 30%) and CD138+ cells (< 10%) assessed using Annexin-V/propidium iodide. Limited effect was observed in cell cycle profile or growth in cell lines. However, DNA synthesis was decreased by 70% at 3 μM (all time points) in U266 though this was not observed in MM.1S. In accordance, immunoblot analyses revealed no change in transcription (c-Myc and H3),

or apoptotic (Bad) proteins that are substrates of Pim kinases. In contrast, autophagy, assessed using acridine orange staining, was induced with SGI-1776 treatment in both cell lines (U266, 25%-70%; MM.1S, 8%-52%) and CD138+ cells (19%-21%). Immunoblot analyses of the autophagy LC3b marker and translation initiation proteins (phospho-p70S6K and 4E-BP1) corroborated autophagy induction. CONCLUSION: These data indicate that SGI-1776 treatment in myeloma cell lines and CD138+ myeloma cells elicits its deleterious effects through inhibition of translation and induction of autophagy.

[1096]

TÍTULO / TITLE: - Nuclear translocation of B-cell-specific transcription factor, BACH2, modulates ROS mediated cytotoxic responses in mantle cell lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 2;8(8):e69126. doi: 10.1371/journal.pone.0069126. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0069126](#)

AUTORES / AUTHORS: - Chen Z; Pittman EF; Romaguera J; Fayad L; Wang M; Neelapu SS; McLaughlin P; Kwak L; McCarty N

INSTITUCIÓN / INSTITUTION: - Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) University of Texas-Health Science Center at Houston, Houston, Texas, United States of America.

RESUMEN / SUMMARY: - BACH2, a B-cell specific transcription factor, plays a critical role in oxidative stress-mediated apoptosis. Bortezomib (Velcade™) is widely used to treat relapsed mantle cell lymphoma (MCL) patients despite varying clinical outcomes. As one of the potential mechanisms of action, bortezomib was reported to elicit endoplasmic reticulum (ER) stress which triggers reactive oxygen species (ROS). In the present study, we investigated the redox-sensitive intracellular mechanism that might play a critical role in bortezomib response in MCL cells. We demonstrated that in MCL cells that are sensitive to bortezomib treatments, BACH2 was translocated to the nucleus in response to bortezomib and induced apoptotic responses through the modulation of anti-oxidative and anti-apoptotic genes. On the other hand, in bortezomib resistant cells, BACH2 expression was confined in the cytoplasm and no suppression of antiapoptotic or antioxidative genes, Nrf2, Gss, CAT, HO-1 and MCL1, was detected. Importantly, levels of BACH2 were significantly higher in bortezomib sensitive MCL patient cells, indicating that BACH2 levels could be an indicator for clinical bortezomib responses. BACH2 translocation to the cytoplasm after phosphorylation was inhibited by PI3K inhibitors and combinatory regimens of bortezomib and PI3K inhibitors sensitized MCL cells to bortezomib. These data suggest that cellular distribution of BACH2 in response to ROS determines the threshold for the induction of apoptosis. Therapies that inhibit BACH2 phosphorylation could be the key for increasing bortezomib cytotoxic response in patients.

[1097]

TÍTULO / TITLE: - Effect of STAT5 silenced by siRNA on proliferation apoptosis and invasion of esophageal carcinoma cell line Eca-109.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Diagn Pathol. 2013 Aug 5;8(1):132. doi: 10.1186/1746-1596-8-132.

●● Enlace al texto completo (gratis o de pago) [1186/1746-1596-8-132](#)

AUTORES / AUTHORS: - Yang Q; Li M; Wang T; Xu H; Zang W; Zhao G

INSTITUCIÓN / INSTITUTION: - Medical Examination Center, The First Affiliated Hospital of Henan University of TCM, Zhengzhou, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: STAT is the backward position of cytokine and growth factor receptors in the nucleus, STAT dimers could bind to DNA and induce transcription of specific target genes. Several lines of evidence support the important roles of STAT, especially STAT5, in carcinogenesis. The overexpression of STAT 5 is related to the differentiation and apoptosis of tumor cells. However, the role of STAT5 in esophageal squamous cell carcinoma remains unclear. METHODS: The siRNA vectors aiming to STAT5 gene were constructed. STAT5 siRNA was transfected into Eca-109 cells by Lipofectamine2000. Expression of STAT5Bcl-2 and Cyclin D1 were analyzed by Western blot and RT-PCR. Eca-109 cells proliferation was determined by MTT. Eca-109 cell cycle and apoptosis were detected by the flow cytometry. Boyden chamber was used to evaluate the invasion and metastasis capabilities of Eca-109 cells. RESULTS: The double strands oligonucleotide of siRNA aiming to STAT5 was successfully cloned into the pRNAT-U6.1 vector, and the target sequence coincided with the design. RT-PCR and Western blotting detection demonstrated that the expression levels of STAT5Bcl-2 and Cyclin D1 gene were obviously decreased in Eca-109 cells transfected with STAT5 siRNA. STAT5 siRNA could suppress the proliferation of Eca-109 cells. The proportion of S and G2/M period frequency was significantly decreased ($p < 0.05$). The proportion of G0/G1 period frequency was significantly increased ($p < 0.05$). The average amount of cells penetrating Matrigel was significantly decreased ($p < 0.05$). CONCLUSIONS: STAT5 silenced by siRNA could induce the apoptosis and suppress the proliferation invasion and metastasis of esophageal carcinoma cell line Eca-109, which indicated STAT5 might be a novel therapeutic strategy for the human ESCC. VIRTUAL SLIDES: The virtual slide(s) for this article can be found here:

diagnosticpathology.diagnomx.eu/vs/1351913072103000.

[1098]

TÍTULO / TITLE: - Concurrent MEK2 Mutation and BRAF Amplification Confer Resistance to BRAF and MEK Inhibitors in Melanoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Rep. 2013 Sep 26;4(6):1090-9. doi:

10.1016/j.celrep.2013.08.023. Epub 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1016/j.celrep.2013.08.023](http://dx.doi.org/10.1016/j.celrep.2013.08.023)

AUTORES / AUTHORS: - Villanueva J; Infante JR; Krepler C; Reyes-Urbe P; Samanta M; Chen HY; Li B; Swoboda RK; Wilson M; Vultur A; Fukunaba-Kalabis M; Wubbenhorst B; Chen TY; Liu Q; Sproesser K; Demarini DJ; Gilmer TM; Martin AM; Marmorstein R; Schultz DC; Speicher DW; Karakousis GC; Xu W; Amaravadi RK; Xu X; Schuchter LM; Herlyn M; Nathanson KL

INSTITUCIÓN / INSTITUTION: - Molecular and Cellular Oncogenesis Program, Melanoma Research Center, The Wistar Institute, Philadelphia, PA 19104, USA. Electronic address: JVillanueva@wistar.org.

RESUMEN / SUMMARY: - Although BRAF and MEK inhibitors have proven clinical benefits in melanoma, most patients develop resistance. We report a de novo MEK2-Q60P mutation and BRAF gain in a melanoma from a patient who progressed on the MEK inhibitor trametinib and did not respond to the BRAF inhibitor dabrafenib. We also identified the same MEK2-Q60P mutation along with BRAF amplification in a xenograft tumor derived from a second melanoma patient resistant to the combination of dabrafenib and trametinib. Melanoma cells chronically exposed to trametinib acquired concurrent MEK2-Q60P mutation and BRAF-V600E amplification, which conferred resistance to MEK and BRAF inhibitors. The resistant cells had sustained MAPK activation and persistent phosphorylation of S6K. A triple combination of dabrafenib, trametinib, and the PI3K/mTOR inhibitor GSK2126458 led to sustained tumor growth inhibition. Hence, concurrent genetic events that sustain MAPK signaling can underlie resistance to both BRAF and MEK inhibitors, requiring novel therapeutic strategies to overcome it.

[1099]

TÍTULO / TITLE: - Proteasome inhibitors block DNA repair and radiosensitize non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 5;8(9):e73710. doi: 10.1371/journal.pone.0073710.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073710](http://dx.doi.org/10.1371/journal.pone.0073710)

AUTORES / AUTHORS: - Cron KR; Zhu K; Kushwaha DS; Hsieh G; Merzon D; Rameseder J; Chen CC; D'Andrea AD; Kozono D

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America.

RESUMEN / SUMMARY: - Despite optimal radiation therapy (RT), chemotherapy and/or surgery, a majority of patients with locally advanced non-small cell lung cancer (NSCLC) fail treatment. To identify novel gene targets for improved tumor control, we performed whole genome RNAi screens to identify knockdowns that most reproducibly increase NSCLC cytotoxicity. These screens identified several proteasome subunits among top hits, including the topmost hit PSMA1, a component of the core

20 S proteasome. Radiation and proteasome inhibition showed synergistic effects. Proteasome inhibition resulted in an 80-90% decrease in homologous recombination (HR), a 50% decrease in expression of NF-kappaB-inducible HR genes BRCA1 and FANCD2, and a reduction of BRCA1, FANCD2 and RAD51 ionizing radiation-induced foci. IkappaBalpha RNAi knockdown rescued NSCLC radioresistance. Irradiation of mice with NCI-H460 xenografts after inducible PSMA1 shRNA knockdown markedly increased murine survival compared to either treatment alone. Proteasome inhibition is a promising strategy for NSCLC radiosensitization via inhibition of NF-kappaB-mediated expression of Fanconi Anemia/HR DNA repair genes.

[1100]

TÍTULO / TITLE: - DNA microarray reveals different pathways responding to paclitaxel and docetaxel in non-small cell lung cancer cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Clin Exp Pathol. 2013 Jul 15;6(8):1538-48. Print 2013.

AUTORES / AUTHORS: - Che CL; Zhang YM; Zhang HH; Sang YL; Lu B; Dong FS; Zhang LJ; Lv FZ

INSTITUCIÓN / INSTITUTION: - Department of respiratory medicine, First Clinical Medical College affiliated to Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - The wide use of paclitaxel and docetaxel in NSCLC clinical treatment makes it necessary to find biomarkers for identifying patients who can benefit from paclitaxel or docetaxel. In present study, NCI-H460, a NSCLC cell line with different sensitivity to paclitaxel and docetaxel, was applied to DNA microarray expression profiling analysis at different time points of lower dose treatment with paclitaxel or docetaxel. And the complex signaling pathways regulating the drug response were identified, and several novel sensitivity-related markers were biocomputed. The dynamic changes of responding genes showed that paclitaxel effect is acute but that of docetaxel is durable at least for 48 hours in NCI-H460 cells. Functional annotation of the genes with altered expression showed that genes/pathways responding to these two drugs were dramatically different. Gene expression changes induced by paclitaxel treatment were mainly enriched in actin cytoskeleton (ACTC1, MYL2 and MYH2), tyrosine-protein kinases (ERRB4, KIT and TIE1) and focal adhesion pathway (MYL2, IGF1 and FLT1), while the expression alterations responding to docetaxel were highly co-related to cell surface receptor linked signal transduction (SHH, DRD5 and ADM2), cytokine-cytokine receptor interaction (IL1A and IL6) and cell cycle regulation (CCNB1, CCNE2 and PCNA). Moreover, we also confirmed some different expression patterns with real time PCR. Our study will provide the potential biomarkers for paclitaxel and docetaxel-selection therapy in clinical application.

[1101]

TÍTULO / TITLE: - HSP90 Inhibitor SNX5422/2112 Targets the Dysregulated Signal and Transcription Factor Network and Malignant Phenotype of Head and Neck Squamous Cell Carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Transl Oncol. 2013 Aug 1;6(4):429-41. Print 2013 Aug.

AUTORES / AUTHORS: - Friedman JA; Wise SC; Hu M; Gouveia C; Vander Broek R; Freudlsperger C; Kannabiran VR; Arun P; Mitchell JB; Chen Z

INSTITUCIÓN / INSTITUTION: - Tumor Biology Section, Head and Neck Surgery Branch, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD.

RESUMEN / SUMMARY: - Heat shock protein 90 (HSP90) is a chaperone protein that stabilizes proteins involved in oncogenic and therapeutic resistance pathways of epithelial cancers, including head and neck squamous cell carcinomas (HNSCCs). Here, we characterized the molecular, cellular, and preclinical activity of HSP90 inhibitor SNX5422/2112 in HNSCC overexpressing HSP90. SNX2112 inhibited proliferation, induced G2/M block, and enhanced cytotoxicity, chemosensitivity, and radiosensitivity between 25 and 250 nM in vitro. SNX2112 showed combinatorial activity with paclitaxel in wild-type (wt) TP53-deficient and cisplatin in mutant (mt) TP53 HNSCC lines. SNX2112 decreased expression or phosphorylation of epidermal growth factor receptor (EGFR), c-MET, v-akt murine thymoma viral oncogene homolog 1 (AKT), extracellular signal-regulated kinases (ERK) 1 and 2, inhibitor kappaB kinase, and signal transducer and transcription factor 3 (STAT3), corresponding downstream nuclear factor kappaB, activator protein-1, and STAT3 reporter genes, and target oncogenes and angiogenic cytokines. Furthermore, SNX2112 enhanced re-expression of TP53 and targets p21WAF1 and PUMA, while TP53 inhibitor Pifithrin or siRNA attenuated the antiproliferative activity of SNX2112 in wtTP53 HNSCC in vitro. Prodrug SNX5422 similarly down-modulated key signal targets, enhanced TP53 expression and apoptosis, and inhibited proliferation, angiogenesis, and tumorigenesis in a wtTP53-deficient HNSCC xenograft model. Thus, HSP90 inhibitor SNX5422/2112 broadly modulates multiple key nodes within the dysregulated signaling network, with corresponding effects upon the malignant phenotype. Our data support investigation of SNX5422/2112 in combination with paclitaxel, cisplatin, and radiotherapy in HNSCC with different TP53 status.

[1102]

TÍTULO / TITLE: - The significance of galectin-3 as a new basal cell marker in prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Aug 1;4:e753. doi: 10.1038/cddis.2013.277.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cddis.2013.277](#)

AUTORES / AUTHORS: - Wang Y; Balan V; Gao X; Reddy PG; Kho D; Tait L; Raz A

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Karmanos Cancer Institute, School of Medicine, Wayne State University, Detroit, MI 48201, USA.

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RESUMEN / SUMMARY: - Prostate cancer may originate from distinct cell types, resulting in the heterogeneity of this disease. Galectin-3 (Gal-3) and androgen receptor (AR) have been reported to play important roles in the progression of prostate cancer, and their heterogeneous expressions might be associated with different cancer subtypes. Our study found that in various prostate cancer cell lines Gal-3 expression was always opposite to AR expression and other luminal cell markers but consistent with basal cell markers including glutathione S-transferase-pi and Bcl-2. This expression pattern was confirmed in human prostate cancer tissues. Our results also showed that prostate cancer cells positive with basal cell markers were more aggressive. Downregulation of Gal-3 expression resulted in increased apoptotic potential and decreased metastasis potential of prostate cancer cells. Our findings demonstrate for the first time that Gal-3 may serve as a new marker for basal characteristics of prostate cancer epithelium. This study helps us to better understand the heterogeneity of prostate cancer. The clinical significance of this study lies in the application of Gal-3 to distinguish prostate cancer subtypes and improve treatment efficacy with designed personalized therapy.

[1103]

TÍTULO / TITLE: - Stem cell-like ALDH cellular states in EGFR-mutant non-small cell lung cancer: A novel mechanism of acquired resistance to erlotinib targetable with the natural polyphenol silibinin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Cycle. 2013 Sep 17;12(21).

AUTORES / AUTHORS: - Corominas-Faja B; Oliveras-Ferraro C; Cuyas E; Segura-Carretero A; Joven J; Martin-Castillo B; Barrajon-Catalan E; Micol V; Bosch-Barrera J; Menendez JA

INSTITUCIÓN / INSTITUTION: - Metabolism & Cancer Group; Translational Research Laboratory; Catalan Institute of Oncology; Girona, Catalonia, España; Girona Biomedical Research Institute (IDIBGI); Girona, Catalonia, España.

RESUMEN / SUMMARY: - The enrichment of cancer stem cell (CSC)-like cellular states has not previously been considered to be a causative mechanism in the generalized progression of EGFR-mutant non-small cell lung carcinomas (NSCLC) after an initial response to the EGFR tyrosine kinase inhibitor erlotinib. To explore this possibility, we utilized a pre-clinical model of acquired erlotinib resistance established by growing NSCLC cells containing a TKI-sensitizing EGFR exon 19 deletion (DeltaE746-A750) in the continuous presence of high doses of erlotinib. Genome-wide analyses using Agilent 44K Whole Human Genome Arrays were evaluated via bioinformatics analyses through GSEA-based screening of the KEGG pathway database to identify the molecular circuitries that were over-represented in the transcriptomic signatures of erlotinib-

refractory cells. The genomic spaces related to erlotinib resistance included a preponderance of cell cycle genes (E2F1, - 2, CDC2, -6) and DNA replication-related genes (MCM4, - 5, - 6, - 7), most of which are associated with early lung development and poor prognosis. In addition, metabolic genes such as ALDH1A3 (a candidate marker for lung cancer cells with CSC-like properties) were identified. Thus, we measured the proportion of erlotinib-resistant cells expressing very high levels of aldehyde dehydrogenase (ALDH) activity attributed to ALDH1/3 isoforms. Using flow cytometry and the ALDEFLUOR® reagent, we confirmed that erlotinib-refractory cell populations contained drastically higher percentages (> 4500%) of ALDHbright cells than the parental erlotinib-responsive cells. Notably, strong decreases in the percentages of ALDHbright cells were observed following incubation with silibinin, a bioactive flavonolignan that can circumvent erlotinib resistance in vivo. The number of lung cancer spheres was drastically suppressed by silibinin in a dose-dependent manner, thus confirming the ability of this agent to inhibit the self-renewal of erlotinib-refractory CSC-like cells. This report is the first to show that: (1) loss of responsiveness to erlotinib in EGFR-mutant NSCLC can be explained in terms of erlotinib-refractory ALDHbright cells, which have been shown to exhibit stem cell-like properties; and (2) erlotinib-refractory ALDHbright cells are sensitive to the natural agent silibinin. Our findings highlight the benefit of administration of silibinin in combination with EGFR TKIs to target CSCs and minimize the ability of tumor cells to escape cell death in EGFR-mutant NSCLC patients.

[1104]

TÍTULO / TITLE: - Apoptotic activities in soft tissue sarcoma: immunohistochemical study and their association with tumour characteristics.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Malays J Med Sci. 2013 Mar;20(2):10-6.

AUTORES / AUTHORS: - Win TT; Yusuf Y; Jaafar H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia.

RESUMEN / SUMMARY: - BACKGROUND: Many studies on the role of apoptosis in cancer development and management have been undertaken. Apoptotic activity depends partly on the balance between anti-apoptotic (Bcl-2) and pro-apoptotic (Bax) activities. This study compared Bcl-2 and Bax expression in the tumour cells and endothelial cells of tumour blood vessels in soft tissue sarcoma, and examined the association of these with tumour characteristics. METHODS: A cross sectional (retrospective) study was conducted on 101 cases of various types of soft tissue sarcoma tumour cells and endothelial cells of tumour blood vessels. The immunohistochemical expressions of Bcl-2 and Bax were compared by correlating them according to site, size, depth, tumour margin, lymph node involvement, and histological type. RESULTS: Higher Bax than Bcl-2 expression in tumour cells was observed, although the difference was not

statistically significant. There was a significant direct association between Bcl-2 and Bax in tumour cells with endothelial cells. Among tumour characteristics, the only significant correlation was that of the Bcl-2 expression in tumour cells with tumour histological subtypes (synovial sarcoma and leiomyosarcoma). CONCLUSION: The findings in this study support the role of endothelial cells in the survival and regression of tumour cells in tumour genesis. Therefore, inhibition of endothelial cell survival and activation, or induction of tumour cell apoptosis offers a promising prospect for tumour management.

[1105]

TÍTULO / TITLE: - The aqueous extract of *Ficus religiosa* induces cell cycle arrest in human cervical cancer cell lines SiHa (HPV-16 Positive) and apoptosis in HeLa (HPV-18 positive).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 26;8(7):e70127. doi: 10.1371/journal.pone.0070127. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0070127](https://doi.org/10.1371/journal.pone.0070127)

AUTORES / AUTHORS: - Choudhari AS; Suryavanshi SA; Kaul-Ghanekar R

INSTITUCIÓN / INSTITUTION: - Cell and Translational Research Laboratory, Interactive Research School for Health Affairs (IRSHA), Bharati Vidyapeeth University Medical College Campus, Dhankawadi, Pune, India.

RESUMEN / SUMMARY: - Natural products are being extensively explored for their potential to prevent as well as treat cancer due to their ability to target multiple molecular pathways. *Ficus religiosa* has been shown to exert diverse biological activities including apoptosis in breast cancer cell lines. In the present study, we report the anti-neoplastic potential of aqueous extract of *F. religiosa* (FRAq) bark in human cervical cancer cell lines, SiHa and HeLa. FRAq altered the growth kinetics of SiHa (HPV-16 positive) and HeLa (HPV-18 positive) cells in a dose-dependent manner. It blocked the cell cycle progression at G1/S phase in SiHa that was characterized by an increase in the expression of p53, p21 and pRb proteins with a simultaneous decrease in the expression of phospho Rb (ppRb) protein. On the other hand, in HeLa, FRAq induced apoptosis through an increase in intracellular Ca^{2+} leading to loss of mitochondrial membrane potential, release of cytochrome-c and increase in the expression of caspase-3. Moreover, FRAq reduced the migration as well as invasion capability of both the cervical cancer cell lines accompanied with downregulation of MMP-2 and Her-2 expression. Interestingly, FRAq reduced the expression of viral oncoproteins E6 and E7 in both the cervical cancer cell lines. All these data suggest that *F. religiosa* could be explored for its chemopreventive potential in cervical cancer.

[1106]

TÍTULO / TITLE: - WWOX suppresses autophagy for inducing apoptosis in methotrexate-treated human squamous cell carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 5;4:e792. doi: 10.1038/cddis.2013.308.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.308](#)

AUTORES / AUTHORS: - Tsai CW; Lai FJ; Sheu HM; Lin YS; Chang TH; Jan MS; Chen SM; Hsu PC; Huang TT; Huang TC; Sheen MC; Chen ST; Chang WC; Chang NS; Hsu LJ

INSTITUCIÓN / INSTITUTION: - Department of Microbiology and Immunology, National Cheng Kung University Medical College, Tainan, Taiwan.

RESUMEN / SUMMARY: - Squamous cell carcinoma (SCC) cells refractory to initial chemotherapy frequently develop disease relapse and distant metastasis. We show here that tumor suppressor WW domain-containing oxidoreductase (WWOX) (also named FOR or WOX1) regulates the susceptibility of SCC to methotrexate (MTX) in vitro and cure of SCC in MTX therapy. MTX increased WWOX expression, accompanied by caspase activation and apoptosis, in MTX-sensitive SCC cell lines and tumor biopsies. Suppression by a dominant-negative or small interfering RNA targeting WWOX blocked MTX-mediated cell death in sensitive SCC-15 cells that highly expressed WWOX. In stark contrast, SCC-9 cells expressed minimum amount of WWOX protein and resisted MTX-induced apoptosis. Transiently overexpressed WWOX sensitized SCC-9 cells to apoptosis by MTX. MTX significantly downregulated autophagy-related Beclin-1, Atg12-Atg5 and LC3-II protein expression and autophagosome formation in the sensitive SCC-15, whereas autophagy remained robust in the resistant SCC-9. Mechanistically, WWOX physically interacted with mammalian target of rapamycin (mTOR), which potentiated MTX-increased phosphorylation of mTOR and its downstream substrate p70 S6 kinase, along with dramatic downregulation of the aforementioned proteins in autophagy, in SCC-15. When WWOX was knocked down in SCC-15, MTX-induced mTOR signaling and autophagy inhibition were blocked. Thus, WWOX renders SCC cells susceptible to MTX-induced apoptosis by dampening autophagy, and the failure in inducing WWOX expression leads to chemotherapeutic drug resistance.

[1107]

TÍTULO / TITLE: - 5-Demethyltangeretin inhibits human nonsmall cell lung cancer cell growth by inducing G2/M cell cycle arrest and apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Nutr Food Res. 2013 Aug 8. doi: 10.1002/mnfr.201300136.

●● Enlace al texto completo (gratis o de pago) [1002/mnfr.201300136](#)

AUTORES / AUTHORS: - Charoensinphon N; Qiu P; Dong P; Zheng J; Ngauv P; Cao Y; Li S; Ho CT; Xiao H

INSTITUCIÓN / INSTITUTION: - Department of Food Science, University of Massachusetts, Amherst, MA, USA.

RESUMEN / SUMMARY: - SCOPE: Tangeretin (TAN) and 5-demethyltangeretin (5DT) are two closely related polymethoxyflavones found in citrus fruits. We investigated growth inhibitory effects on three human nonsmall cell lung cancer (NSCLC) cells. METHODS AND RESULTS: Cell viability assay demonstrated that 5DT inhibited NSCLC cell growth in a time- and dose-dependent manner, and IC50 s of 5DT were 79-fold, 57-fold, and 56-fold lower than those of TAN in A549, H460, and H1299 cells, respectively. Flow cytometry analysis showed that 5DT induced extensive G2/M cell cycle arrest and apoptosis in NSCLC cells, while TAN at tenfold higher concentrations did not. The apoptosis induced by 5DT was further confirmed by activation of caspase-3 and cleavage of PARP. Moreover, 5DT dose-dependently upregulated p53 and p21Cip1/Waf1, and downregulated Cdc-2 (Cdk-1) and cyclin B1. HPLC analysis revealed that the intracellular levels of 5DT in NSCLC cells were 2.7-4.9 fold higher than those of TAN after the cells were treated with 5DT or TAN at the same concentration. CONCLUSION: Our results demonstrated that 5DT inhibited NSCLC cell growth by inducing G2/M cell cycle arrest and apoptosis. These effects were much stronger than those produced by TAN, which is partially due to the higher intracellular uptake of 5DT than TAN.

[1108]

TÍTULO / TITLE: - PIAS1-modulated Smad2/4 complex activation is involved in zinc-induced cancer cell apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 19;4:e811. doi: 10.1038/cddis.2013.333.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.333](#)

AUTORES / AUTHORS: - Yang N; Zhao B; Rasul A; Qin H; Li J; Li X

INSTITUCIÓN / INSTITUTION: - The Key Laboratory of Molecular Epigenetics of MOE, Institute of Genetics and Cytology, Northeast Normal University, Changchun 130024, China.

RESUMEN / SUMMARY: - Prostate cancer is one of the most frequently diagnosed cancers among men. Dietary intake of nutrients is considered crucial for preventing the initiation of events leading to the development of carcinoma. Many dietary compounds have been considered to contribute to cancer prevention including zinc, which has a pivotal role in modulating apoptosis. However, the mechanism for zinc-mediated prostate cancer chemoprevention remains enigmatic. In this study, we investigated the therapeutic effect of zinc in prostate cancer chemoprevention for the first time. Exposure to zinc induced apoptosis and resulted in transactivation of p21(WAF1/Cip1) in a Smad-dependent and p53-independent manner in prostate cancer cells. Smad2 and PIAS1 proteins were significantly upregulated resulting in dramatically increased interactions between Smad2/4 and PIAS1 in the presence of zinc in LNCaP cells. Furthermore, it was found that the zinc-induced Smad4/2/PIAS1 transcriptional complex is responsible for Smad4 binding to SBE1 and SBE3 regions

within the p21(WAF1/Cip1) promoter. Exogenous expression of Smad2/4 and PIAS1 promotes zinc-induced apoptosis concomitant with Smad4 nuclear translocation, whereas endogenous Smad2/4 silencing inhibited zinc-induced apoptosis accompanying apparent p21(WAF1/Cip1) reduction. Moreover, the knockdown of PIAS1 expression attenuated the zinc-induced recruitment of Smad4 on the p21(WAF1/Cip1) promoter. The colony formation experiments demonstrate that PIAS1 and Smad2/4 silencing could attenuate zinc apoptotic effects, with a proliferation of promoting effects. We further demonstrate the correlation of apoptotic sensitivity to zinc and Smad4 and PIAS1 in multiple cancer cell lines, demonstrating that the important roles of PIAS1, Smad2, and Smad4 in zinc-induced cell death and p21(WAF1/Cip1) transactivation were common biological events in different cancer cell lines. Our results suggest a new avenue for regulation of zinc-induced apoptosis, and provide a model that demonstrates zinc endorses the Smad2/4/PIAS1 complex to activate the p21(WAF1/Cip1) gene that mediates apoptosis.

[1109]

TÍTULO / TITLE: - Protective Effect of Melatonin on Methamphetamine-Induced Apoptosis in Glioma Cell Line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neurotox Res. 2013 Aug 23.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s12640-013-9419-y](#)

AUTORES / AUTHORS: - Jumnonprakon P; Govitrapong P; Tocharus C; Tungkum W; Tocharus J

INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand.

RESUMEN / SUMMARY: - Methamphetamine (METH) is a highly addictive drug causing neurodegenerative diseases. METH has been known to be neurotoxic by inducing oxidative stress, free radical, and pro-inflammatory cytokines. Previous studies have shown that METH could induce neuron and glial cell death, especially inducing glial cell-mediated neurotoxicity that plays a critical role in stress-induced central nervous system damage. Therefore, the aim of the present study is to explore the mechanisms of METH-induced cell death in the glial cell. METH-induced glial cells death is mediated via mitochondrial damage pathway. METH activates the upregulation of the Bax, cytochrome c, cleavage caspase 9 and 3 proteins, and downregulation of Bcl-XL protein in cascade. Pretreatment with melatonin, a neurohormone secreted by the pineal gland, effectively reduced glial cell death. Moreover, melatonin increased the Bcl-XL/Bax ratio but reduced the level of cytochrome c, cleavage caspase 9 and 3 proteins. Therefore, these results demonstrated that melatonin could reduce the cytotoxic effect of METH by decreasing the mitochondrial death pathway activation in glial cells. This outcome suggests that melatonin might be beneficial as the neuroprotection in neurodegenerative diseases caused by METH or other pathogens.

[1110]

TÍTULO / TITLE: - Sulphamoylated 2-methoxyestradiol analogues induce apoptosis in adenocarcinoma cell lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 5;8(9):e71935. doi: 10.1371/journal.pone.0071935.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0071935](https://doi.org/10.1371/journal.pone.0071935)

AUTORES / AUTHORS: - Visagie M; Theron A; Mqoco T; Vieira W; Prudent R; Martinez A; Lafanechere L; Joubert A

INSTITUCIÓN / INSTITUTION: - Department of Physiology, University of Pretoria, Pretoria, South Africa.

RESUMEN / SUMMARY: - 2-Methoxyestradiol (2ME2) is a naturally occurring estradiol metabolite which possesses antiproliferative, antiangiogenic and antitumor properties. However, due to its limited biological accessibility, synthetic analogues have been synthesized and tested in attempt to develop drugs with improved oral bioavailability and efficacy. The aim of this study was to evaluate the antiproliferative effects of three novel in silico-designed sulphamoylated 2ME2 analogues on the HeLa cervical adenocarcinoma cell line and estrogen receptor-negative breast adenocarcinoma MDA-MB-231 cells. A dose-dependent study (0.1-25 µM) was conducted with an exposure time of 24 hours. Results obtained from crystal violet staining indicated that 0.5 µM of all 3 compounds reduced the number of cells to 50%. Lactate dehydrogenase assay was used to assess cytotoxicity, while the mitotracker mitochondrial assay and caspase-6 and -8 activity assays were used to investigate the possible occurrence of apoptosis. Tubulin polymerization assays were conducted to evaluate the influence of these sulphamoylated 2ME2 analogues on tubulin dynamics. Double immunofluorescence microscopy using labeled antibodies specific to tyrosinated and detyrosinated tubulin was conducted to assess the effect of the 2ME2 analogues on tubulin dynamics. An insignificant increase in the level of lactate dehydrogenase release was observed in the compounds-treated cells. These sulphamoylated compounds caused a reduction in mitochondrial membrane potential, cytochrome c release and caspase 3 activation indicating apoptosis induction by means of the intrinsic pathway in HeLa and MDA-MB-231 cells. Microtubule depolymerization was observed after exposure to these three sulphamoylated analogues.

[1111]

TÍTULO / TITLE: - Anti-Lung Cancer Activity through Enhancement of Immunomodulation and Induction of Cell Apoptosis of Total Triterpenes Extracted from Ganoderma lucidum (Leyss. ex Fr.) Karst.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Molecules. 2013 Aug 19;18(8):9966-81. doi: 10.3390/molecules18089966.

●● Enlace al texto completo (gratis o de pago) [3390/molecules18089966](https://doi.org/10.3390/molecules18089966)

AUTORES / AUTHORS: - Feng L; Yuan L; Du M; Chen Y; Zhang MH; Gu JF; He JJ; Wang Y; Cao W

INSTITUCIÓN / INSTITUTION: - Key Laboratory of New Drug Delivery Systems of Chinese Materia Medica, Jiangsu Provincial Academy of Chinese Medicine, Nanjing 210028, Jiangsu, China. ychen202@hotmail.com.

RESUMEN / SUMMARY: - Ganoderma lucidum (Leyss. ex Fr.) Karst. (GLK) has been used traditionally for the prevention and treatment of cancers or tumors for a long time in Traditional Chinese Medicine. The triterpenes as main effective components of GLK have been found to be beneficial for the efficacy. The purpose of this study was to examine the anti-lung cancer activity of triterpenes of GLK in vitro and in vivo and to explore their anti-lung cancer effects and potential mechanisms. A549 cells and Lewis tumor-bearing mice were used to evaluate the inhibition effects of triterpenes on cell proliferation and tumor growth. The IC50 of triterpenes of GLK on A549 cells was 24.63 µg/mL. Triterpenes of GLK could significantly inhibit tumor growth in mice (30, 60 and 120 mg/kg). The immune organs indexes including spleen and thymus were increased remarkably by the treatment with triterpenes. Moreover, they were able to stimulate the immune response by increasing the expressions of IL-6 and TNF-α. Flow cytometric analysis revealed that cell arrest caused by triterpenes treatment (7.5, 15 and 30 µg/mL) was in the G2/M phase in A549 cells. Triterpenes induced apoptosis by decreasing the expression of the antiapoptotic protein Bcl-2 and pro-caspase 9 and increasing the levels of cleaved-caspase 9. Our findings suggested that the triterpenes of GLK have anti-lung cancer activity in vitro and in vivo via enhancement of immunomodulation and induction of cell apoptosis. The study provides insights into the mechanism of GLK in the prevention and treatment of lung cancer.

[1112]

TÍTULO / TITLE: - Ligand and structure-based classification models for Prediction of P-glycoprotein inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Chem Inf Model. 2013 Sep 19.

●● Enlace al texto completo (gratis o de pago) [1021/ci400289j](https://doi.org/10.1021/ci400289j)

AUTORES / AUTHORS: - Klepsch F; Poongavanam V; Ecker GF

RESUMEN / SUMMARY: - The ABC transporter P-glycoprotein (P-gp) actively transports a wide range of drugs and toxins out of cells, and is therefore related to multidrug resistance and the ADME profile of therapeutics. Thus, development of predictive in silico models for the identification of P-gp inhibitors is of great interest in the field of drug discovery and development. So far in-silico P-gp inhibitor prediction was

dominated by ligand-based approaches, due to the lack of high-quality structural information about P-gp. The present study aims at comparing the P-gp inhibitor/non-inhibitor classification performance obtained by docking into a homology model of P-gp, to supervised machine learning methods, such as Kappa nearest neighbor, support vector machine (SVM), random forest and binary QSAR, by using a large, structurally diverse data set. In addition, the applicability domain of the models was assessed using an algorithm based on Euclidean distance. Results show that random forest and SVM performed best for classification of P-gp inhibitors and non-inhibitors, correctly predicting 73/75 % of the external test set compounds. Classification based on the docking experiments using the scoring function ChemScore resulted in the correct prediction of 61 % of the external test set. This demonstrates that ligand-based models currently remain the methods of choice for accurately predicting P-gp inhibitors. However, structure-based classification offers information about possible drug/protein interactions, which helps in understanding the molecular basis of ligand-transporter interaction and could therefore also support lead optimization.

[1113]

TÍTULO / TITLE: - Molecular dynamics simulation of complex Histones Deacetylase (HDAC) Class II Homo Sapiens with suberoylanilide hydroxamic acid (SAHA) and its derivatives as inhibitors of cervical cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Bioinformation. 2013 Jul 17;9(13):696-700. doi: 10.6026/97320630009696. Print 2013.

●● Enlace al texto completo (gratis o de pago) [6026/97320630009696](#)

AUTORES / AUTHORS: - Tambunan US; Bakri R; Prasetya T; Parikesit AA; Kerami D

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, Faculty of Mathematics and Science, University of Indonesia, Depok 16424 Indonesia.

RESUMEN / SUMMARY: - Cervical cancer is second most common cancer in woman worldwide. Cervical cancer caused by human papillomavirus (HPV) oncogene. Inhibition of histone deacetylase (HDAC) activity has been known as a potential strategy for cancer therapy. SAHA is an HDAC inhibitor that has been used in cancer therapy but still has side effects. SAHA modification proposed to minimize side effects. Triazole attachment on the chain of SAHA has been known to enhance the inhibition ability of SAHA and less toxic. In this study, it will be carried out with molecular dynamic simulations of SAHA modifications consisting ligand 1^a, 2^a and, 2c to interact with six HDAC in hydrated conditions. To all six HDAC Class II, performed docking with SAHA and a modified inhibitor. The docking results were then carried out molecular dynamics simulations to determine the inhibitor affinities in hydrated conditions. The molecular dynamic simulations results show better affinities of ligand 2c with HDAC 4, 6, and 7 than SAHA itself, and good affinity was also shown by ligand 2^a and 1c on HDAC 5 and 9. The results of this study can be a reference to obtain better inhibitors.

[1114]

TÍTULO / TITLE: - Predicting anticancer peptides with Chou's pseudo amino acid composition and investigating their mutagenicity via Ames test.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Theor Biol. 2013 Sep 10. pii: S0022-5193(13)00419-0. doi: 10.1016/j.jtbi.2013.08.037.

●● Enlace al texto completo (gratis o de pago) [1016/j.itbi.2013.08.037](#)

AUTORES / AUTHORS: - Hajisharifi Z; Piryaeie M; Mohammad Beigi M; Behbahani M; Mohabatkar H

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Faculty of Advanced Sciences and Technologies, University of Isfahan, Isfahan, Iran.

RESUMEN / SUMMARY: - Cancer is an important reason of death worldwide. Traditional cytotoxic therapies, such as radiation and chemotherapy, are expensive and cause severe side effects. Currently, design of anticancer peptides is a more effective way for cancer treatment. So there is a need to develop a computational method for predicting the anticancer peptides. In the present study, two methods have been developed to predict these peptides using support vector machine (SVM) as a powerful machine learning algorithm. Classifiers have been applied based on the concept of Chou's pseudo-amino acid composition (PseAAC) and local alignment kernel. Since a number of HIV-1 proteins have cytotoxic effect, therefore we predicted the anticancer effect of HIV-1 p24 protein with these methods. After the prediction, mutagenicity of 2 anticancer peptides and 2 non-anticancer peptides was investigated by Ames test. Our results show that, the accuracy and the specificity of local alignment kernel based method are 89.7% and 92.68%, respectively. The accuracy and specificity of PseAAC-based method are 83.82% and 85.36%, respectively. By computational analysis, out of 22 peptides of p24 protein, 4 peptides are anticancer and 18 are non-anticancer. In the Ames test results, it is clear that anticancer peptides (ARP788.8 and ARP788.21) are not mutagenic. Therefore the results demonstrate that the described computation methods are useful to identify potential anticancer peptides, which are worthy of further experimental validation and 2 peptides (ARP788.8 and ARP788.21) of HIV-1 p24 protein can be used as new anticancer candidates without mutagenicity. \$!''998.95\$!" TATATAT - J Theor Biol

[1115]

TÍTULO / TITLE: - Tackling gliomas with nanoformulated antineoplastic drugs: suitability of hyaluronic acid nanoparticles.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Transl Oncol. 2013 Sep 27.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1114-1](#)

AUTORES / AUTHORS: - Ganau M

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Engineering, University of Cagliari, Cagliari, Italy, mario.ganau@singularityu.org.

[1116]

TÍTULO / TITLE: - Preclinical screening of histone deacetylase inhibitors combined with ABT-737, rhTRAIL/MD5-1 or 5-azacytidine using syngeneic Vk*MYC multiple myeloma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Sep 12;4:e798. doi: 10.1038/cddis.2013.306.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.306](https://doi.org/10.1038/cddis.2013.306)

AUTORES / AUTHORS: - Matthews GM; Lefebure M; Doyle MA; Shortt J; Ellul J; Chesi M; Banks KM; Vidacs E; Faulkner D; Atadja P; Bergsagel PL; Johnstone RW

INSTITUCIÓN / INSTITUTION: - 1] Gene Regulation Laboratory, Cancer Therapeutics, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria, Australia [2] Sir Peter MacCallum Department of Oncology, University of Melbourne, East Melbourne, VIC, Australia.

RESUMEN / SUMMARY: - Multiple myeloma (MM) is an incurable malignancy with an unmet need for innovative treatment options. Histone deacetylase inhibitors (HDACi) are a new class of anticancer agent that have demonstrated activity in hematological malignancies. Here, we investigated the efficacy and safety of HDACi (vorinostat, panobinostat, romidepsin) and novel combination therapies using in vitro human MM cell lines and in vivo preclinical screening utilizing syngeneic transplanted Vk*MYC MM. HDACi were combined with ABT-737, which targets the intrinsic apoptosis pathway, recombinant human tumour necrosis factor-related apoptosis-inducing ligand (rhTRAIL/MD5-1), that activates the extrinsic apoptosis pathway or the DNA methyl transferase inhibitor 5-azacytidine. We demonstrate that in vitro cell line-based studies provide some insight into drug activity and combination therapies that synergistically kill MM cells; however, they do not always predict in vivo preclinical efficacy or toxicity. Importantly, utilizing transplanted Vk*MYC MM, we report that panobinostat and 5-azacytidine synergize to prolong the survival of tumor-bearing mice. In contrast, combined HDACi/rhTRAIL-based strategies, while efficacious, demonstrated on-target dose-limiting toxicities that precluded prolonged treatment. Taken together, our studies provide evidence that the transplanted Vk*MYC model of MM is a useful screening tool for anti-MM drugs and should aid in the prioritization of novel drug testing in the clinic.

[1117]

TÍTULO / TITLE: - A tumor-penetrating Peptide modification enhances the antitumor activity of thymosin alpha 1.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 19;8(8):e72242. doi: 10.1371/journal.pone.0072242.

●● Enlace al texto completo (gratuito o de pago) [1371/journal.pone.0072242](https://doi.org/10.1371/journal.pone.0072242)

AUTORES / AUTHORS: - Lao X; Liu M; Chen J; Zheng H

INSTITUCIÓN / INSTITUTION: - Department of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiang Su Province, P.R. China.

RESUMEN / SUMMARY: - A serious limitation of numerous antitumor drugs is the incapacity to penetrate solid tumors. However, addition of an RGD fragment to peptide drugs might solve this problem. In this study, we explored whether the introduction of a permeability-enhancing sequence, such as iRGD (CRGDK/RGPD/EC) fragments, would enhance the activity of thymosin alpha 1 (Talpha1). The modified Talpha1 (Talpha1-iRGD) was successfully expressed and purified, and the in vitro assay showed that Talpha1-iRGD presented a similar activity as Talpha1 in promoting proliferation of mouse splenocytes. Meanwhile, cell adhesion analysis revealed that Talpha1-iRGD exhibited more specific and greater binding with tumor cells compared with Talpha1. Furthermore, the iRGD fragment evidently enhanced the basal ability of Talpha1 to inhibit proliferation of cancer cells in vitro, particularly of mouse melanoma cell line B16F10 and human lung cancer cell line H460. Our findings indicated that the addition of an iRGD fragment increased the anti-proliferative activity of Talpha1 against cancer cells by improving the ability of Talpha1 to penetrate the tumor cells. This study highlighted the important roles of an iRGD sequence in the therapeutic strategy of Talpha1-iRGD. Thus, Talpha1-iRGD could be a novel drug candidate for cancer treatment.

[1118]

TÍTULO / TITLE: - Tumor-penetrating peptide functionalization enhances the anti-glioblastoma effect of doxorubicin liposomes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nanotechnology. 2013 Oct 11;24(40):405101. doi: 10.1088/0957-4484/24/40/405101. Epub 2013 Sep 12.

●● Enlace al texto completo (gratuito o de pago) [1088/0957-4484/24/40/405101](https://doi.org/10.1088/0957-4484/24/40/405101)

AUTORES / AUTHORS: - Yang Y; Yan Z; Wei D; Zhong J; Liu L; Zhang L; Wang F; Wei X; Xie C; Lu W; He D

INSTITUCIÓN / INSTITUTION: - School of Materials Science and Engineering, Shanghai Jiao Tong University, Shanghai 200240, People's Republic of China. National Engineering Research Center for Nanotechnology, Shanghai 200241, People's Republic of China.

RESUMEN / SUMMARY: - The targeted therapeutic effect of nano drug delivery system for glioblastoma has been hampered by the weak enhanced permeability and retention (EPR) effect of glioblastoma and the low delivering efficiency of NDDS in glioblastoma tissue. In this study, a tumor-penetrating peptide (RGERPPR), the specific ligand of neuropilin-1 overexpressed on glioblastoma and endothelial cells, was used as a targeting moiety to enhance the anti-glioblastoma effect of doxorubicin liposomes.

Firstly, RGERPPR-PEG-DSPE was synthesized and used to prepare the RGERPPR peptide-functionalized liposomes (RGE-LS), which showed vesicle sizes of around 90 nm and narrow size distributions. The cellular uptake and in vivo near-infrared fluorescence imaging test displayed that RGE-LS exhibited increased uptake by glioblastoma cells and intracranial glioblastoma tissues. The cytotoxicity assay and anti-glioblastoma study proved that RGERPPR functionalization significantly enhanced the in vitro inhibitory effect of doxorubicin liposomes on glioblastoma cells and prolonged the median survival time of nude mice bearing intracranial glioblastoma. Finally, the immunofluorescence analysis evidenced that RGE-LS were able to penetrate through tumor vessels and stroma and deep into the whole tumor tissue. The results indicated that tumor-penetrating peptide functionalization is an effective strategy for enhancing the anti-glioblastoma effect of doxorubicin liposomes.

[1119]

TÍTULO / TITLE: - Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Discov. 2013 Sep 25.

●● Enlace al texto completo (gratis o de pago) [1158/2159-8290.CD-13-0314](#)

AUTORES / AUTHORS: - Walter AO; Tjin Tham Sjin R; Haringsma HJ; Ohashi K; Sun J; Lee K; Dubrovskiy A; Labenski M; Zhu Z; Wang Z; Sheets M; St Martin T; Karp R; van Kalken D; Chaturvedi P; Niu D; Nacht M; Petter RC; Westlin W; Lin K; Jaw-Tsai S; Raponi M; Van Dyke T; Etter J; Weaver Z; Pao W; Singh J; Simmons AD; Harding TC; Allen A

INSTITUCIÓN / INSTITUTION: - 1Translational Medicine, Clovis Oncology, Inc.

RESUMEN / SUMMARY: - Non-small cell lung cancer (NSCLC) patients with activating epidermal growth factor receptor (EGFR) mutations initially respond to first generation reversible EGFR tyrosine kinase inhibitors. However, clinical efficacy is limited by acquired resistance, frequently driven by the EGFR T790M mutation. CO-1686 is a novel, irreversible and orally delivered kinase inhibitor that specifically targets the mutant forms of EGFR including T790M while exhibiting minimal activity towards the wild-type (WT) receptor. Oral administration of CO-1686 as single agent induces tumor regression in EGFR mutated NSCLC tumor xenograft and transgenic models. Minimal activity of CO-1686 against the WT EGFR receptor was observed. In NSCLC cells with acquired resistance to CO-1686 in vitro, there was no evidence of additional mutations or amplification of the EGFR gene, but resistant cells exhibited signs of epithelial-mesenchymal transition (EMT) and demonstrated increased sensitivity to AKT inhibitors. These results suggest CO-1686 may offer a novel therapeutic option for patients with mutant EGFR NSCLC.

[1120]

TÍTULO / TITLE: - Telomerase contributes to fludarabine resistance in primary human leukemic lymphocytes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e70428. doi: 10.1371/journal.pone.0070428. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0070428

AUTORES / AUTHORS: - Shawi M; Chu TW; Martinez-Marignac V; Yu Y; Gryaznov SM; Johnston JB; Lees-Miller SP; Assouline SE; Autexier C; Aloyz R

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Experimental Medicine, McGill University, Montreal, Quebec, Canada.

RESUMEN / SUMMARY: - We report that Imetelstat, a telomerase inhibitor that binds to the RNA component of telomerase (hTR), can sensitize primary CLL lymphocytes to fludarabine in vitro. This effect was observed in lymphocytes from clinically resistant cases and with cytogenetic abnormalities associated with bad prognosis. Imetelstat mediated-sensitization to fludarabine was not associated with telomerase activity, but with the basal expression of Ku80. Since both Imetelstat and Ku80 bind hTR, we assessed 1) if Ku80 and Imetelstat alter each other's binding to hTR in vitro and 2) the effect of an oligonucleotide complementary to the Ku binding site in hTR (Ku oligo) on the survival of primary CLL lymphocytes exposed to fludarabine. We show that Imetelstat interferes with the binding of Ku70/80 (Ku) to hTR and that the Ku oligo can sensitize CLL lymphocytes to FLU. Our results suggest that Ku binding to hTR may contribute to fludarabine resistance in CLL lymphocytes. This is the first report highlighting the potentially broad effectiveness of Imetelstat in CLL, and the potential biological and clinical implications of a functional interaction between Ku and hTR in primary human cancer cells.

[1121]

TÍTULO / TITLE: - Ron knockdown and Ron monoclonal antibody IMC-RON8 sensitize pancreatic cancer to histone deacetylase inhibitors (HDACi).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 29;8(7):e69992. doi: 10.1371/journal.pone.0069992. Print 2013.

●● Enlace al texto completo (gratis o de pago) 1371/journal.pone.0069992

AUTORES / AUTHORS: - Zou Y; Howell GM; Humphrey LE; Wang J; Brattain MG

INSTITUCIÓN / INSTITUTION: - Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, Nebraska, United States of America.

RESUMEN / SUMMARY: - Recepteur d'origine nantais (Ron) is overexpressed in a panel of pancreatic cancer cells and tissue samples from pancreatic cancer patients. Ron can be activated by its ligand macrophage stimulating protein (MSP), thereby activating oncogenic signaling pathways. Crosstalk between Ron and EGFR, c-Met, or IGF-1R may provide a mechanism underlying drug resistance. Thus, targeting Ron may represent a

novel therapeutic strategy. IMC-RON8 is the first Ron monoclonal antibody (mAb) entering clinical trial for targeting Ron overexpression. Our studies show IMC-RON8 downmodulated Ron expression in pancreatic cancer cells and significantly blocked MSP-stimulated Ron activation, downstream Akt and ERK phosphorylation, and survivin mRNA expression. IMC-RON8 hindered MSP-induced cell migration and reduced cell transformation. Histone deacetylase inhibitors (HDACi) are reported to target expression of various genes through modification of nucleosome histones and non-histone proteins. Our work shows HDACi TSA and Panobinostat (PS) decreased Ron mRNA and protein expression in pancreatic cancer cells. PS also reduced downstream signaling of pAkt, survivin, and XIAP, as well as enhanced cell apoptosis. Interestingly, PS reduced colony formation in Ron knockdown cells to a greater extent than Ron scramble control cells in colony formation and soft agarose assays. IMC-RON8 could also sensitize pancreatic cancer cells to PS, as reflected by reduced colony numbers and size in combination treatment with IMC-RON8 and PS compared to single treatment alone. The co-treatment further reduced Ron expression and pAkt, and increased PARP cleavage compared to either treatment alone. This study suggests the potential for a novel combination approach which may ultimately be of value in treatment of pancreatic cancer.

[1122]

TÍTULO / TITLE: - Polymer-conjugated inhibitors of tumor necrosis factor-alpha for local control of inflammation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomatter. 2013 Jul 10;3(3). pii: e25597.

AUTORES / AUTHORS: - Washburn NR; Prata JE; Friedrich EE; Ramadan MH; Elder AN; Sun LT

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Engineering; Carnegie Mellon University; Pittsburgh, PA USA; Department of Chemistry; Carnegie Mellon University; Pittsburgh, PA USA.

RESUMEN / SUMMARY: - Burns, chronic wounds, osteoarthritis, and uveitis are examples of conditions characterized by local, intense inflammatory responses that can impede healing or even further tissue degradation. The most powerful anti-inflammatory drugs available are often administered systemically, but these carry significant side effects and are not compatible for patients that have underlying complications associated with their condition. Conjugation of monoclonal antibodies that neutralize pro-inflammatory cytokines to high molecular weight hydrophilic polymers has been shown to be an effective strategy for local control of inflammation. Lead formulations are based on antibody inhibitors of tumor necrosis factor-alpha conjugated to hyaluronic acid having molecular weight greater than 1 MDa. This review will discuss fundamental aspects of medical conditions that could be treated with these conjugates and design principles for preparing these cytokine-neutralizing polymer conjugates.

Results demonstrating that infliximab, an approved inhibitor of tumor necrosis factor- α , can be incorporated into the conjugates using a broad range of water-soluble polymers are also presented, along with a prospectus for clinical translation.

[1123]

TÍTULO / TITLE: - Selectively Targeting Prostate Cancer with Antiandrogen Equipped Histone Deacetylase Inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ACS Chem Biol. 2013 Sep 20.

●● [Enlace al texto completo \(gratis o de pago\) 1021/cb400542w](#)

AUTORES / AUTHORS: - Gryder BE; Akbashev MJ; Rood MK; Raftery ED; Meyers WM; Dillard P; Khan S; Oyelere AK

INSTITUCIÓN / INSTITUTION: - Parker H. Petit Institute for Bioengineering & Biosciences, Department of Chemistry and Biochemistry, Georgia Institute of Technology , 315 Ferst Dr. NW, Atlanta, Georgia 30332-0230, United States.

RESUMEN / SUMMARY: - Diverse cellular processes relevant to cancer progression are regulated by the acetylation status of proteins. Among such processes is chromatin remodeling via histone proteins, controlled by opposing histone deacetylase (HDAC) and histone acetyltransferase (HAT) enzymes. Histone deacetylase inhibitors (HDACi) show great promise in preclinical cancer models, but clinical trials treating solid tumors have failed to improve patient survival. This is due in part to an inability of HDACi to effectively accumulate in cancerous cells. To address this problem we designed HDACi with secondary pharmacophores to facilitate selective accumulation in malignant cells. We present the first example of HDACi compounds targeted to prostate tumors by equipping them with the additional ability to bind the androgen receptor (AR) with nonsteroidal antiandrogen moieties. Leads among these new dual-acting molecules bind to the AR and halt AR transcriptional activity at lower concentrations than clinical antiandrogens. They inhibit key isoforms of HDAC with low nanomolar potency. Fluorescent microscopy reveals varying degrees of AR nuclear localization in response to these compounds that correlates with their HDAC activity. These biological properties translate into potent anticancer activity against hormone-dependent (AR+) LNCaP and to a lesser extent against hormone-independent (AR-) DU145 prostate cancer, while having greatly reduced toxicity in noncancerous cells. This illustrates that engaging multiple biological targets with a single chemical probe can achieve both potent and cell-type-selective responses.

[1124]

TÍTULO / TITLE: - Inferences from the ADMET analysis of predicted inhibitors to Follicle Stimulating Hormone in the context of infertility.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Bioinformation. 2013 Aug 28;9(15):788-91. doi: 10.6026/97320630009788.

●● Enlace al texto completo (gratis o de pago) [6026/97320630009788](https://doi.org/10.6026/97320630009788)

AUTORES / AUTHORS: - Bhogireddy N; Veeramachaneni GK; Ambatipudi NV; Mathi P; Ippaguntla J; Ganta UR; Adusumalli SG; Bokka VR

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Centre for Biomedical Research, KLU University, Vaddeswaram, Guntur district-522 502.

RESUMEN / SUMMARY: - Follicle stimulating hormone (FSH) is a glycoprotein secreted by gonadotrophs of the anterior pituitary gland that regulates reproduction in mammals. FSH targets its receptor (FSHR) expressed only on granulosa cells and induce the maturation of ovarian follicles in females. The levels of both FSH and FSHR rise until the middle of estrus cycle and then falls on level at the time of ovulation. It is associated with stimulated sertoli cell proliferation in testes and supports spermatogenesis in males. The interaction between the polypeptide FSH hormone and its corresponding receptor is highly selective. Therefore, it is of interest to inhibit FSH in the context of infertility. The structure of FSH (PDB ID: 1XWD) is screened using molecular docking techniques against the ZINC database (a database of 2.7 million compounds) with reference to known standard compounds. This exercise identifies compounds with better binding and ADMET (Absorption, Digestion, Metabolism, Excretion and Toxicity) properties compared to known standard compounds. These observations find application for the consideration of such compounds for further validation towards inhibiting the FSH.

[1125]

TÍTULO / TITLE: - Hyaluronan and N-ERC/Mesothelin as Key Biomarkers in a Specific Two-Step Model to Predict Pleural Malignant Mesothelioma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Aug 21;8(8):e72030. doi: 10.1371/journal.pone.0072030.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072030](https://doi.org/10.1371/journal.pone.0072030)

AUTORES / AUTHORS: - Mundt F; Nilsson G; Arslan S; Csuros K; Hillerdal G; Yildirim H; Metintas M; Dobra K; Hjerpe A

INSTITUCIÓN / INSTITUTION: - Division of Pathology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden.

RESUMEN / SUMMARY: - PURPOSE: Diagnosis of malignant mesothelioma is challenging. The first available diagnostic material is often an effusion and biochemical analysis of soluble markers may provide additional diagnostic information. This study aimed to establish a predictive model using biomarkers from pleural effusions, to allow early and accurate diagnosis. PATIENTS AND METHODS: Effusions were collected prospectively from 190 consecutive patients at a regional referral centre. Hyaluronan, N-ERC/mesothelin, C-ERC/mesothelin, osteopontin, syndecan-1, syndecan-2, and

thioredoxin were measured using ELISA and HPLC. A predictive model was generated and validated using a second prospective set of 375 effusions collected consecutively at a different referral centre. RESULTS: Biochemical markers significantly associated with mesothelioma were hyaluronan (odds ratio, 95% CI: 8.82, 4.82-20.39), N-ERC/mesothelin (4.81, 3.19-7.93), CERC/mesothelin (3.58, 2.43-5.59) and syndecan-1 (1.34, 1.03-1.77). A two-step model using hyaluronan and N-ERC/mesothelin, and combining a threshold decision rule with logistic regression, yielded good discrimination with an area under the ROC curve of 0.99 (95% CI: 0.97-1.00) in the model generation dataset and 0.83 (0.74-0.91) in the validation dataset, respectively. CONCLUSIONS: A two-step model using hyaluronan and N-ERC/mesothelin predicts mesothelioma with high specificity. This method can be performed on the first available effusion and could be a useful adjunct to the morphological diagnosis of mesothelioma.

[1126]

TÍTULO / TITLE: - Array analysis for potential biomarker of gemcitabine identification in non-small cell lung cancer cell lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Clin Exp Pathol. 2013 Aug 15;6(9):1734-46.

AUTORES / AUTHORS: - Zhang HH; Zhang ZY; Che CL; Mei YF; Shi YZ

INSTITUCIÓN / INSTITUTION: - Department of rheumatism and immunology, First Clinical Medical College affiliated to Harbin Medical University Harbin, China.

RESUMEN / SUMMARY: - Gemcitabine is one of the most widely used drugs for the treatment of advanced Non-small cell lung cancer (NSCLC), but modest objective response rate of patients to gemcitabine makes it necessary to identify novel biomarkers for patients who can benefit from gemcitabine-based therapy and to improve the effect of clinical therapy. In this work, 3 NSCLC cell lines displaying different sensitivities to gemcitabine were applied for mRNA and microRNA (miR) expression chips to figure out the biomarkers for gemcitabine sensitivity. Genes whose expression increased dramatically in sensitive cell lines were mainly enriched in cell adhesion (NRP2, CXCR3, CDK5R1, IL32 and CDH2) and secretory granule (SLC11A1, GP5, CD36 and IGF1), while genes with significantly upregulated expression in resistant cell line were mainly clustered in methylation modification (HIST1H2BF, RAB23 and TP53) and oxidoreductase (TP53I3, CYP27B1 and SOD3). The most intriguing is the activation of Wnt/beta-catenin signaling in gemcitabine resistant NSCLC cell lines. The miR-155, miR-10^a, miR-30^a, miR-24-2* and miR-30c-2* were upregulated in sensitive cell lines, while expression of miR-200c, miR-203, miR-885-5p, miR-195 and miR-25* was increased in resistant cell line. Genes with significantly altered expression and putatively mediated by the expression-changed miRs were mainly enriched in chromatin assembly (MAF, HLF, BCL2, and IGSF3), anti-apoptosis (BCL2, IGF1 and IKBKB), protein kinase (NRP2, PAK7 and CDK5R1) (all the above genes were

upregulated in sensitive cells) and small GTPase mediated signal transduction (GNA13, RAP2A, ARHGAP5 and RAB23, down-regulated in sensitive cells). Our results might provide potential biomarkers for gemcitabine sensitivity prediction and putative targets to overcome gemcitabine resistance in NSCLC patients.

[1127]

TÍTULO / TITLE: - EGFR Exon-Level Biomarkers of the Response to Bevacizumab/Erlotinib in Non-Small Cell Lung Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 10;8(9):e72966. doi: 10.1371/journal.pone.0072966.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0072966](https://doi.org/10.1371/journal.pone.0072966)

AUTORES / AUTHORS: - Baty F; Rothschild S; Fruh M; Betticher D; Droge C; Cathomas R; Rauch D; Gautschi O; Bubendorf L; Crowe S; Zappa F; Pless M; Brutsche M

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary Medicine, Cantonal Hospital, St. Gallen, Switzerland.

RESUMEN / SUMMARY: - Activating epidermal growth factor receptor (EGFR) mutations are recognized biomarkers for patients with metastatic non-small cell lung cancer (NSCLC) treated with EGFR tyrosine kinase inhibitors (TKIs). EGFR TKIs can also have activity against NSCLC without EGFR mutations, requiring the identification of additional relevant biomarkers. Previous studies on tumor EGFR protein levels and EGFR gene copy number revealed inconsistent results. The aim of the study was to identify novel biomarkers of the response to TKIs in NSCLC by investigating whole genome expression at the exon-level. We used exon arrays and clinical samples from a previous trial (SAKK19/05) to investigate the expression variations at the exon-level of 3 genes potentially playing a key role in modulating treatment response: EGFR, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and vascular endothelial growth factor (VEGFA). We identified the expression of EGFR exon 18 as a new predictive marker for patients with untreated metastatic NSCLC treated with bevacizumab and erlotinib in the first line setting. The overexpression of EGFR exon 18 in tumor was significantly associated with tumor shrinkage, independently of EGFR mutation status. A similar significant association could be found in blood samples. In conclusion, exonic EGFR expression particularly in exon 18 was found to be a relevant predictive biomarker for response to bevacizumab and erlotinib. Based on these results, we propose a new model of EGFR testing in tumor and blood.

[1128]

TÍTULO / TITLE: - Association between Plasma Levels of Plasminogen Activator Inhibitor-1 and Colorectal Neoplasms.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Gut Liver. 2013 Sep;7(5):519-23. doi: 10.5009/gnl.2013.7.5.519. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [5009/gnl.2013.7.5.519](https://doi.org/10.5009/gnl.2013.7.5.519)

AUTORES / AUTHORS: - Kim ER; Yang MH; Lim YJ; Lee JH; Chang DK; Kim YH; Son HJ; Kim JJ; Rhee JC; Kim JY

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND/AIMS: Plasminogen activator inhibitor-1 (PAI-1) is important for tumor growth, Invasion, and metastasis. In this study, we investigated the relationship between plasma levels of PAI-1 and colorectal adenomas. METHODS: We reviewed the medical records of 3,136 subjects who underwent colonoscopy as a screening exam. The subjects were classified into a case group with adenomas (n=990) and a control group (n=2,146). Plasma PAI-1 levels were categorized into three groups based on tertile. RESULTS: The plasma levels of PAI-1 were significantly higher in adenoma cases than in controls (p=0.023). The prevalence of colorectal adenomas increased significantly with increasing levels of PAI-1 (p=0.038). In the adenoma group, advanced pathologic features, size, and number of adenomas did not differ among the three groups based on tertiles for plasma PAI-1 levels. Using multivariate analysis, we found that plasma level of PAI-1 was not associated with the risk of colorectal adenomas (p=0.675). Adjusted odds ratios for colorectal adenomas according to increasing plasma levels of PAI-1 were 0.980 (95% confidence interval [CI], 0.768 to 1.251) for the second-highest plasma level and 1.091 (95% CI, 0.898 to 1.326) for the highest level, compared with the lowest levels. CONCLUSIONS: These results suggest that elevated plasma PAI-1 levels are not associated with the risk of colorectal neoplasms.

[1129]

TÍTULO / TITLE: - Targeting an Achilles' heel of cancer with a WRN helicase inhibitor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Cycle. 2013 Sep 12;12(20).

AUTORES / AUTHORS: - Aggarwal M; Banerjee T; Sommers JA; Brosh RM

INSTITUCIÓN / INSTITUTION: - Laboratory of Molecular Gerontology; National Institute on Aging; National Institutes of Health; NIH Biomedical Research Center; Baltimore, MD USA.

RESUMEN / SUMMARY: - Our recently published work suggests that DNA helicases such as the Werner syndrome helicase (WRN) represent a novel class of proteins to target for anticancer therapy. Specifically, pharmacological inhibition of WRN helicase activity in human cells defective in the Fanconi anemia (FA) pathway of interstrand cross-link (ICL) repair are sensitized to the DNA cross-linking agent and chemotherapy drug mitomycin C (MMC) by the WRN helicase inhibitor NSC 617145. 1 The mechanistic basis for the synergistic interaction between NSC 617145 and MMC is discussed in this

paper and extrapolated to potential implications for genetic or chemically induced synthetic lethality provoked by cellular exposure to the WRN helicase inhibitor under the context of relevant DNA repair deficiencies associated with cancers or induced by small-molecule inhibitors. Experimental data are presented showing that small-molecule inhibition of WRN helicase elevates sensitivity to MMC-induced stress in human cells that are deficient in both FANCD2 and DNA protein kinase catalytic subunit (DNA-PKcs). These findings suggest a model in which drug-mediated inhibition of WRN helicase activity exacerbates the deleterious effects of MMC-induced DNA damage when both the FA and NHEJ pathways are defective. We conclude with a perspective for the FA pathway and synthetic lethality and implications for DNA repair helicase inhibitors that can be developed for anticancer strategies.

[1130]

TÍTULO / TITLE: - Development of interferon gamma-based immunocytokines targeting renal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncoimmunology. 2013 Jul 1;2(7):e24964. Epub 2013 May 16.

●● Enlace al texto completo (gratis o de pago) [4161/onci.24964](#)

AUTORES / AUTHORS: - Chen P; Balachandran S

INSTITUCIÓN / INSTITUTION: - Immune Cell Development and Host Defense Program; Fox Chase Cancer Center; Philadelphia, PA USA.

RESUMEN / SUMMARY: - Advanced renal cancer is an incurable malignancy in need of novel therapeutic avenues. We have generated interferon gamma (IFN γ)-based fusion antibodies (immunocytokines) that target CD70, a putative biomarker of renal cancer. These immunocytokines efficiently labeled renal cancer cells, and, when combined with the proteasome inhibitor bortezomib, killed them by activating a RIP1-dependent necrotic pathway.

[1131]

TÍTULO / TITLE: - The HDAC Inhibitor LBH589 Induces ERK-Dependent Prometaphase Arrest in Prostate Cancer via HDAC6 Inactivation and Down-Regulation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Sep 4;8(9):e73401. doi: 10.1371/journal.pone.0073401.

●● Enlace al texto completo (gratis o de pago) [1371/journal.pone.0073401](#)

AUTORES / AUTHORS: - Chuang MJ; Wu ST; Tang SH; Lai XM; Lai HC; Hsu KH; Sun KH; Sun GH; Chang SY; Yu DS; Hsiao PW; Huang SM; Cha TL

INSTITUCIÓN / INSTITUTION: - Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC.

RESUMEN / SUMMARY: - Histone deacetylase inhibitors (HDACIs) have potent anti-cancer activity in a variety of cancer models. Understanding the molecular mechanisms

involved in the therapeutic responsiveness of HDACi is needed before its clinical application. This study aimed to determine if a potent HDACi, LBH589 (Panobinostat), had differential therapeutic responsiveness towards LNCaP and PC-3 prostate cancer (PCa) cells. The former showed prometaphase arrest with subsequent apoptosis upon LBH589 treatment, while the latter was less sensitive and had late G2 arrest. The LBH589 treatment down-regulated HDAC6 and sustained ERK activation, and contributed to prometaphase arrest. Mechanistically, LBH589 inhibited HDAC6 activity, caused its dissociation from protein phosphatase PP1alpha, and increased 14-3-3zeta acetylation. Acetylated 14-3-3zeta released its mask effect on serine 259 of c-Raf and serine 216 of Cdc25C subsequent to de-phosphorylation by PP1alpha, which contributed to ERK activation. Enhanced ERK activity by LBH589 further down-regulated HDAC6 protein levels and sustained ERK activation by free-forward regulation. The sustained Cdc25C and ERK activation resulted in early M-phase (prometaphase) arrest and subsequent apoptosis in the most sensitive LNCaP cells but not in PC-3 cells. This study provides pre-clinical evidence that HDAC6 may serve as a sensitive therapeutic target in the treatment of prostate cancer with HDACi LBH589 for clinical translation. This study also posits a novel mechanism of HDAC6 participation in regulating the c-Raf-PP1-ERK signaling pathway and contributing to M phase cell-cycle transition.

[1132]

TÍTULO / TITLE: - MicroRNA Profile to Predict Gemcitabine Resistance in Bladder Carcinoma Cell Lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genes Cancer. 2013 Jan;4(1-2):61-9. doi: 10.1177/1947601913484495.

- Enlace al texto completo (gratis o de pago) [1177_1947601913484495](#) [pii]
- Enlace al texto completo (gratis o de pago) [1177/1947601913484495](#)

AUTORES / AUTHORS: - Kozinn SI; Harty NJ; Delong JM; Deliyannis C; Logvinenko T; Summerhayes IC; Libertino JA; Holway AH; Rieger-Christ KM

INSTITUCIÓN / INSTITUTION: - Department of Urology, Lahey Clinic, Burlington, MA, USA.

RESUMEN / SUMMARY: - MicroRNAs (miRNA) are small, noncoding RNAs with important regulatory roles in development, differentiation, cell proliferation, and death as well as the complex process of acquired drug resistance. The goal of this study was to identify specific miRNAs and their potential protein targets that confer acquired resistance to gemcitabine in urothelial carcinoma of the bladder (UCB) cell lines. Gemcitabine-resistant cells were established from 6 cell lines following exposure to escalating concentrations of the drug and by passaging cells in the presence of the drug over a 2- to 3-month period. Differential miRNA expression was identified in a microarray format comparing untreated controls with resistant cell lines, representing the maximum tolerated concentration, and results were validated via qRT-PCR. The

involvement of specific miRNAs in chemoresistance was confirmed with transfection experiments, followed by clonogenic assays and Western blot analysis. Gemcitabine resistance was generated in 6 UCB cell lines. Microarray analysis comparing miRNA expression between gemcitabine-resistant and parental cells identified the differential expression of 66 miRNAs. Confirmation of differential expression was recorded via qRT-PCR in a subset of these miRNAs. Within this group, let-7b and let-7i exhibited decreased expression, while miR-1290 and miR-138 displayed increased expression levels in gemcitabine-resistant cells. Transfection of pre-miR-138 and pre-miR-1290 into parental cells attenuated cell death after exposure to gemcitabine, while transfection of pre-miR-let-7b and pre-miR-let-7i into the resistant cells augmented cell death. Mucin-4 was up-regulated in gemcitabine-resistant cells. Ectopic expression of let-7i and let-7b in the resistant cells resulted in the down-regulation of mucin-4. These results suggest a role for miRNAs 1290, 138, let-7i, and let-7b in imparting resistance to gemcitabine in UCB cell lines in part through the modulation of mucin-4. Alterations in these miRNAs and/or mucin-4 may constitute a potential therapeutic strategy for improving the efficacy of gemcitabine in UCB.

[1133]

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Bosn J Basic Med Sci. 2013 Aug;13(3):186-91.

AUTORES / AUTHORS: - Aghbali A; Hosseini SV; Delazar A; Gharavi NK; Shahneh FZ; Orangi M; Bandehagh A; Baradaran B

INSTITUCIÓN / INSTITUTION: - Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Tabriz University of Medical Sciences, Daneshgah street 51666-14766, Tabriz, Iran.

RESUMEN / SUMMARY: - Development of novel therapeutic modalities is crucial for the treatment of oral squamous cell carcinoma (OSCC). Recent scientific studies have been focused on herbal medicines as potent anti-cancer drug candidates. This study is the first to investigate the cytotoxic effects and the mechanism of cell death induced by grape seed extract (GSE) in oral squamous cell carcinoma (KB cells). MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and trypan blue assays were performed in KB cells as well as human umbilical vein endothelial cells (HUVEC) were used to analyze the cytotoxic activity of GSE. Furthermore, the apoptosis-inducing action of the extract was determined by TUNEL, DNA fragmentation and cell death analysis. Statistical significance was determined by analysis of variance (ANOVA), followed by Duncan's test at a significance level of $P \leq 0.05$. The results showed apoptotic potential of GSE, confirmed by significant inhibition of cell growth and viability in a dose- and time- dependent manner without inducing damage to non-cancerous cell line HUVEC. The results of this study suggest that this plant contains potential bioactive compound(s) for the treatment of oral squamous cell carcinoma.

[1134]

TÍTULO / TITLE: - Genome-wide association studies on prostate cancer: the end or the beginning?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Protein Cell. 2013 Aug 27.

●● Enlace al texto completo (gratis o de pago) [1007/s13238-013-3055-4](#)

AUTORES / AUTHORS: - Chen R; Ren S; Sun Y

INSTITUCIÓN / INSTITUTION: - Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, 200433, China.

RESUMEN / SUMMARY: - Prostate cancer (PCa) is the second most frequently diagnosed malignancy in men. Genome-wide association studies (GWAS) has been highly successful in discovering susceptibility loci for prostate cancer. Currently, more than twenty GWAS have identified more than fifty common variants associated with susceptibility with PCa. Yet with the increase in loci, voices from the scientific society are calling for more. In this review, we summarize current findings, discuss the common problems troubling current studies and shed light upon possible breakthroughs in the future. GWAS is the beginning of something wonderful. Although we are quite near the end of the beginning, post-GWAS studies are just taking off and future studies are needed extensively. It is believed that in the future GWAS information will be helpful to build a comprehensive system intergraded with PCa prevention, diagnosis, molecular classification, personalized therapy.

[1135]

TÍTULO / TITLE: - Resveratrol and P-glycoprotein Inhibitors Enhance the Anti-skin Cancer Effects of Ursolic Acid.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Res. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1158/1541-7786.MCR-13-0237](#)

AUTORES / AUTHORS: - Junco JJ; Mancha A; Malik G; Wei SJ; Kim DJ; Liang H; Slaga TJ

INSTITUCIÓN / INSTITUTION: - The University of Texas Health Science Center at San Antonio.

RESUMEN / SUMMARY: - Ursolic acid (UA), present in apples, rosemary, and other sources, is known to inhibit tumor formation and tumor cell viability in multiple systems, including skin. However, various cancers are resistant to UA treatment. Herein, skin carcinoma cells (Ca3/7) as compared to skin papilloma cells (MT1/2) displayed more resistance to UA-induced cytotoxicity. Interestingly, Ca3/7 cells had elevated levels of P-glycoprotein (P-gp), an ATP-dependent efflux pump that mediates resistance to chemotherapy in pre-clinical and clinical settings, and not only accumulated less but also more rapidly expelled the P-gp substrate Rhodamine 123 (Rh123) indicating UA is transported by P-gp. To determine if P-gp inhibition can

enhance UA-mediated cytotoxicity, cells were challenged with P-gp inhibitors verapamil (VRP) or cyclosporin A (CsA). Alternatively, cells were pre-treated with the natural compound resveratrol (RES), a known chemotherapy sensitizer. VRP and RES enhanced the effects of UA in both cell lines, while CsA only did so in Ca3/7 cells. Similarly, VRP inhibited Rh123 efflux in both lines, while CsA only inhibited Rh123 efflux in Ca3/7 cells. RES did not inhibit Rh123 efflux in either line, indicating the synergistic effects of RES and UA are not manifest by inhibition of P-gp-mediated efflux of UA. These results indicate that the anti-skin cancer effects of UA are enhanced with P-gp inhibitors. In addition, RES and UA interact synergistically, but not through inhibition of P-gp. Implications: Resveratrol and/or p-glycoprotein inhibitors in combination with ursolic acid are an effective anti-skin cancer regimen.

[1136]

TÍTULO / TITLE: - Tumor suppressor function of miR-483-3p on squamous cell carcinomas due to its pro-apoptotic properties.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Cycle. 2013 Jul 15;12(14):2183-93. doi: 10.4161/cc.25330.

●● [Enlace al texto completo \(gratis o de pago\) 4161/cc.25330](#)

AUTORES / AUTHORS: - Bertero T; Bourget-Ponzio I; Puissant A; Loubat A; Mari B; Meneguzzi G; Auberger P; Barbry P; Ponzio G; Rezzonico R

INSTITUCIÓN / INSTITUTION: - CNRS UMR 7275, IPMC, Valbonne, France.

RESUMEN / SUMMARY: - The frequent alteration of miRNA expression in many cancers, together with our recent reports showing a robust accumulation of miR-483-3p at the final stage of skin wound healing, and targeting of CDC25A leading to an arrest of keratinocyte proliferation, led us to hypothesize that miR-483-3p could also be endowed with antitumoral properties. We tested that hypothesis by documenting the in vitro and in vivo impacts of miR-483-3p in squamous cell carcinoma (SCC) cells. miR-483-3p sensitized SCC cells to serum deprivation- and drug-induced apoptosis, thus exerting potent tumor suppressor activities. Its pro-apoptotic activity was mediated by a direct targeting of several anti-apoptotic genes, such as API5, BIRC5, and RAN. Interestingly, an in vivo delivery of miR-483-3p into subcutaneous SCC xenografts significantly hampered tumor growth. This effect was explained by an inhibition of cell proliferation and an increase of apoptosis. This argues for its further use as an adjuvant in the many instances of cancers characterized by a downregulation of miR-483-3p.

[1137]

TÍTULO / TITLE: - Elevated prx1 provides resistance to docetaxel, but is not associated with predictive significance in lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Tuberc Respir Dis (Seoul). 2013 Aug;75(2):59-66. doi: 10.4046/trd.2013.75.2.59. Epub 2013 Aug 30.

●● Enlace al texto completo (gratis o de pago) [4046/trd.2013.75.2.59](#)

AUTORES / AUTHORS: - Hwang KE; Park C; Seol CH; Hwang YR; Hwang JS; Jung JW; Choi KH; Jeong ET; Kim HR

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Institute of Wonkwang Medical Science, Wonkwang University School of Medicine, Iksan, Korea.

RESUMEN / SUMMARY: - BACKGROUND: This study was conducted in order to elucidate the effects of docetaxel on the growth of peroxiredoxin 1 (Prx1) knockdown A549 xenograft tumors and further tested the role of Prx1 as a predictor for how a patient would respond to docetaxel treatment. METHODS: Effects of docetaxel on the growth of scrambled- and shPrx1-infected A549 xenograft tumors in nude mice were measured. Moreover, immunohistochemical expression of Prx1 was evaluated in paraffin-embedded tissues from 24 non-small cell lung cancer patients who had received docetaxel-cisplatin regimens as a first-line treatment. RESULTS: Docetaxel treatment in Prx1 knockdown xenograft tumor resulted in reduced tumors growth compared with other groups. Prx1 knockdown increased the production of cleaved caspases-8 and -9 in the control itself compared to scramble tumors. Moreover, docetaxel treatment in Prx1 knockdown tissue led to an increased protein band. Phosphorylated Akt was found in Prx1 scramble tissues. Phosphorylated FOXO1 was detected in the docetaxel treatment group. On the other hand, Prx1 knockdown completely suppressed the Akt-FOXO1 axis. The median progression-free survival (PFS) of patients with low Prx1 expression was 7 months (95% confidence interval [CI], 6.0-7.7), whereas the median progression-free survival of patients with high Prx1 expression was 4 months (95% CI, 4.0-5.0). However, high Prx1 expression was not associated with decreased PFS (p=0.114). CONCLUSION: Our findings suggest that elevated Prx1 provides resistance to docetaxel treatment through suppression of FOXO1-induced apoptosis in A549 xenograft tumors, but may not be related with the predictive significance for response to docetaxel treatment.

[1138]

TÍTULO / TITLE: - Direct intercalation of cisplatin into zirconium phosphate nanoplatelets for potential cancer nanotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nanoscale. 2013 Sep 26.

●● Enlace al texto completo (gratis o de pago) [1039/c3nr02206d](#)

AUTORES / AUTHORS: - Diaz A; Gonzalez ML; Perez RJ; David A; Mukherjee A; Baez A; Clearfield A; Colon JL

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, University of Puerto Rico, PO Box 23346, Rio Piedras, PR 00931-3346, USA. jorge.colon10@upr.edu.

RESUMEN / SUMMARY: - We report the use of zirconium phosphate (ZrP) nanoplatelets for the encapsulation of the anticancer drug cisplatin and its delivery to tumor cells. Cisplatin was intercalated into ZrP by direct ion exchange and was tested in vitro for

cytotoxicity in the human breast cancer (MCF-7) cell line. The structural characterization of the intercalated cisplatin in ZrP suggests that during the intercalation process, the chloride ligands of the cisplatin complex were substituted by phosphate groups within the layers. Consequently, a new phosphate phase with the platinum complex directly bound to ZrP (cisPt@ZrP) is produced with an interlayer distance of 9.3 Å. The in vitro release profile of the intercalated drug upon a pH stimulus shows that at low pH under lysosomal conditions the platinum complex is released with simultaneous hydrolysis of the zirconium phosphate material, while at higher pH the complex is not released. Experiments with the MCF-7 cell line show that cisPt@ZrP reduced the cell viability up to 40%. The cisPt@ZrP intercalation product is envisioned as a future nanotherapy agent against cancer. Taking advantage of the shape and sizes of the ZrP particles and controlled release of the drug at low pH, it is intended to exploit the enhanced permeability and retention effect of tumors, as well as their intrinsic acidity, for the destruction of malignant cells.
