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

Cancer Pharmacogenomics.

Julio - Agosto 2013 / July - August 2013

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[1]

TÍTULO / TITLE: - N0539 phase II trial of fulvestrant and bevacizumab in patients with metastatic breast cancer previously treated with an aromatase inhibitor: a North Central Cancer Treatment Group (now Alliance) trial.

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

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

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt213](#)

AUTORES / AUTHORS: - Tan WW; Dueck AC; Flynn P; Steen P; Anderson D; Rowland K; Northfelt D; Perez EA

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Mayo Clinic, Jacksonville.

RESUMEN / SUMMARY: - BACKGROUND: Based on preclinical studies, the vascular endothelial pathway is an important mechanism for estrogen receptor resistance. We conducted a phase II study of fulvestrant and bevacizumab in patients with aromatase inhibitor pretreated metastatic breast cancer.

PATIENTS AND METHODS: A single-stage phase II study was conducted with these objectives: 6-month progression-free survival (PFS), tumor response, toxic effect, and overall survival. Regimen: 250 mg fulvestrant days 1 and 15 (cycle 1) then day 1 (cycle 2 and beyond) and 10 mg/kg bevacizumab days 1 and 15 of each 4-week cycle. **RESULTS:** At interim analysis, 20 eligible patients initiated treatment, 11 were progression free and on treatment at 3 months, not meeting the protocol-specified efficacy requirements (at least 12 of 20). Accrual remained open during interim analysis with 36 patients enrolling

before final study closure. Among the 33 eligible patients, the median PFS was 6.2 months [95% confidence interval (CI) 3.6-10.1 months]. Of the 18 with measurable disease, 4 (22%) patients (95% CI 6% to 48%) had a confirmed tumor response (1 complete, 3 partial). The most common grade \geq 3 adverse events were hypertension 3 (9%) and headache 3 (9%). CONCLUSIONS: The fulvestrant/bevacizumab combination is safe and tolerable; however, it did not meet its statistical end point.

[2]

TÍTULO / TITLE: - Retinoic acid and arsenic trioxide for acute promyelocytic leukemia.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jul 11;369(2):111-21. doi: 10.1056/NEJMoa1300874.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1300874](#)

AUTORES / AUTHORS: - Lo-Coco F; Avvisati G; Vignetti M; Thiede C; Orlando SM; Iacobelli S; Ferrara F; Fazi P; Cicconi L; Di Bona E; Specchia G; Sica S; Divona M; Levis A; Fiedler W; Cerqui E; Breccia M; Fioritoni G; Salih HR; Cazzola M; Melillo L; Carella AM; Brandts CH; Morra E; von Lilienfeld-Toal M; Hertenstein B; Wattad M; Lubbert M; Hanel M; Schmitz N; Link H; Kropp MG; Rambaldi A; La Nasa G; Luppi M; Ciceri F; Finizio O; Venditti A; Fabbiano F; Dohner K; Sauer M; Ganser A; Amadori S; Mandelli F; Dohner H; Ehninger G; Schlenk RF; Platzbecker U

INSTITUCIÓN / INSTITUTION: - Dipartimento di Biomedicina e Prevenzione, Università Tor Vergata, Rome, Italy. francesco.lo.coco@uniroma2.it

RESUMEN / SUMMARY: - BACKGROUND: All-trans retinoic acid (ATRA) with chemotherapy is the standard of care for acute promyelocytic leukemia (APL), resulting in cure rates exceeding 80%. Pilot studies of treatment with arsenic trioxide with or without ATRA have shown high efficacy and reduced hematologic toxicity. METHODS: We conducted a phase 3, multicenter trial comparing ATRA plus chemotherapy with ATRA plus arsenic trioxide in patients with APL classified as low-to-intermediate risk (white-cell count, $\leq 10 \times 10^9$ per liter). Patients were randomly assigned to receive either ATRA plus arsenic trioxide for induction and consolidation therapy or standard ATRA-idarubicin induction therapy followed by three cycles of consolidation therapy with ATRA plus chemotherapy and maintenance therapy with low-dose chemotherapy and ATRA. The study was designed as a noninferiority trial to show that the difference between the rates of event-free survival at 2 years in the two groups was not greater than 5%. RESULTS: Complete remission was achieved in all 77 patients in the ATRA-arsenic trioxide group who could be evaluated (100%) and in 75 of 79 patients in the ATRA-chemotherapy group (95%) (P=0.12). The median follow-up was 34.4 months. Two-year event-free survival rates were 97% in the ATRA-arsenic trioxide group and 86% in the ATRA-chemotherapy

group (95% confidence interval for the difference, 2 to 22 percentage points; P<0.001 for noninferiority and P=0.02 for superiority of ATRA-arsenic trioxide). Overall survival was also better with ATRA-arsenic trioxide (P=0.02). As compared with ATRA-chemotherapy, ATRA-arsenic trioxide was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity. CONCLUSIONS: ATRA plus arsenic trioxide is at least not inferior and may be superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk APL. (Funded by Associazione Italiana contro le Leucemie and others; ClinicalTrials.gov number, NCT00482833.).

[3]

TÍTULO / TITLE: - Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jul 4;369(1):32-42. doi: 10.1056/NEJMoa1215637. Epub 2013 Jun 19.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1215637](#)

AUTORES / AUTHORS: - Byrd JC; Furman RR; Coutre SE; Flinn IW; Burger JA; Blum KA; Grant B; Sharman JP; Coleman M; Wierda WG; Jones JA; Zhao W; Heerema NA; Johnson AJ; Sukbuntherng J; Chang BY; Clow F; Hedrick E; Buggy JJ; James DF; O'Brien S

INSTITUCIÓN / INSTITUTION: - Division of Hematology, Department of Internal Medicine, Ohio State University, Columbus, OH 43210, USA.

john.byrd@osumc.edu

RESUMEN / SUMMARY: - BACKGROUND: The treatment of relapsed chronic lymphocytic leukemia (CLL) has resulted in few durable remissions. Bruton's tyrosine kinase (BTK), an essential component of B-cell-receptor signaling, mediates interactions with the tumor microenvironment and promotes the survival and proliferation of CLL cells. METHODS: We conducted a phase 1b-2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib (PCI-32765), a first-in-class, oral covalent inhibitor of BTK designed for treatment of B-cell cancers, in patients with relapsed or refractory CLL or small lymphocytic lymphoma. A total of 85 patients, the majority of whom were considered to have high-risk disease, received ibrutinib orally once daily; 51 received 420 mg, and 34 received 840 mg. RESULTS: Toxic effects were predominantly grade 1 or 2 and included transient diarrhea, fatigue, and upper respiratory tract infection; thus, patients could receive extended treatment with minimal hematologic toxic effects. The overall response rate was the same in the group that received 420 mg and the group that received 840 mg (71%), and an additional 20% and 15% of patients in the respective groups had a partial response with lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies,

and the 17p13.1 deletion. At 26 months, the estimated progression-free survival rate was 75% and the rate of overall survival was 83%. CONCLUSIONS: Ibrutinib was associated with a high frequency of durable remissions in patients with relapsed or refractory CLL and small lymphocytic lymphoma, including patients with high-risk genetic lesions. (Funded by Pharmacyclics and others; ClinicalTrials.gov number, NCT01105247.).

[4]

TÍTULO / TITLE: - Mg²⁺ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D.

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

REVISTA / JOURNAL: - Science. 2013 Jul 12;341(6142):186-91. doi: 10.1126/science.1240094.

●● Enlace al texto completo (gratis o de pago) [1126/science.1240094](https://doi.org/10.1126/science.1240094)

AUTORES / AUTHORS: - Chaigne-Delalande B; Li FY; O'Connor GM; Lukacs MJ; Jiang P; Zheng L; Shatzer A; Biancalana M; Pittaluga S; Matthews HF; Jancel TJ; Bleesing JJ; Marsh RA; Kuijpers TW; Nichols KE; Lucas CL; Nagpal S; Mehmet H; Su HC; Cohen JI; Uzel G; Lenardo MJ

INSTITUCIÓN / INSTITUTION: - Molecular Development of the Immune System Section, Lymphocyte Molecular Genetics Unit, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

RESUMEN / SUMMARY: - The magnesium transporter 1 (MAGT1) is a critical regulator of basal intracellular free magnesium (Mg²⁺) concentrations. Individuals with genetic deficiencies in MAGT1 have high levels of Epstein-Barr virus (EBV) and a predisposition to lymphoma. We show that decreased intracellular free Mg²⁺ causes defective expression of the natural killer activating receptor NKG2D in natural killer (NK) and CD8(+) T cells and impairs cytolytic responses against EBV. Notably, magnesium supplementation in MAGT1-deficient patients restores intracellular free Mg²⁺ and NKG2D while concurrently reducing EBV-infected cells in vivo, demonstrating a link between NKG2D cytolytic activity and EBV antiviral immunity in humans. Moreover, these findings reveal a specific molecular function of free basal intracellular Mg²⁺ in eukaryotic cells.

[5]

TÍTULO / TITLE: - Acquired resistance to crizotinib from a mutation in CD74-ROS1.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jun 20;368(25):2395-401. doi: 10.1056/NEJMoa1215530. Epub 2013 Jun 1.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1215530](https://doi.org/10.1056/NEJMoa1215530)

AUTORES / AUTHORS: - Awad MM; Katayama R; McTigue M; Liu W; Deng YL; Brooun A; Friboulet L; Huang D; Falk MD; Timofeevski S; Wilner KD; Lockerman EL; Khan TM; Mahmood S; Gainor JF; Digumarthy SR; Stone JR; Mino-Kenudson M; Christensen JG; Iafrate AJ; Engelman JA; Shaw AT

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA 02114, USA.

RESUMEN / SUMMARY: - Crizotinib, an inhibitor of anaplastic lymphoma kinase (ALK), has also recently shown efficacy in the treatment of lung cancers with ROS1 translocations. Resistance to crizotinib developed in a patient with metastatic lung adenocarcinoma harboring a CD74-ROS1 rearrangement who had initially shown a dramatic response to treatment. We performed a biopsy of a resistant tumor and identified an acquired mutation leading to a glycine-to-arginine substitution at codon 2032 in the ROS1 kinase domain. Although this mutation does not lie at the gatekeeper residue, it confers resistance to ROS1 kinase inhibition through steric interference with drug binding. The same resistance mutation was observed at all the metastatic sites that were examined at autopsy, suggesting that this mutation was an early event in the clonal evolution of resistance. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.).

[6]

TÍTULO / TITLE: - Tracking tumor resistance using 'liquid biopsies'.

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

REVISTA / JOURNAL: - Nat Med. 2013 Jun;19(6):676-7. doi: 10.1038/nm.3233.

●● Enlace al texto completo (gratis o de pago) [1038/nm.3233](#)

AUTORES / AUTHORS: - Pantel K; Diaz LA Jr; Polyak K

INSTITUCIÓN / INSTITUTION: - Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf, University of Hamburg, Hamburg, Germany.

[7]

TÍTULO / TITLE: - Adding Epoetin Alfa to Intense Dose-Dense Adjuvant Chemotherapy for Breast Cancer: Randomized Clinical Trial.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Jul 17;105(14):1018-1026. Epub 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt145](#)

AUTORES / AUTHORS: - Moebus V; Jackisch C; Schneeweiss A; Huober J; Lueck HJ; du Bois A; Thomssen C; Kurbacher C; Kuhn W; Nitz U; Runnebaum IB; Hinkel A; Kreienberg R; Untch M

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Department of Gynecology and Obstetrics, Klinikum Frankfurt Höchst, Frankfurt, Germany (VM); Department of Gynecology and Obstetrics, Klinikum Offenbach GmbH,

Offenbach, Germany (CJ); National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany (AS); Department of Gynecology and Obstetrics, University of Duesseldorf, Duesseldorf, Germany (JH); Gynakologisch-Onkologische Praxis Hannover, Hannover, Germany (HJL); Department of Gynecology and Gynecologic Oncology, KEM Hussenstift, Essen, Germany (AdB); Department of Gynecology, University of Halle, Halle (Saale), Germany (CT); Medizinisches Zentrum Bonn-Friedensplatz, Bonn, Germany (CK); Department of Gynecology and Obstetrics, University of Bonn, Bonn, Germany (WK); Brustzentrum Niederrhein, Ev. Krankenhaus Bethesda, Monchengladbach, Germany (UN); Department of Gynecology and Obstetrics, University of Jena, Jena, Germany (IBR); WiSP Research Institute, Langenfeld, Germany (AH); Department of Gynecology and Obstetrics, University of Ulm, Ulm, Germany (RK); Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany (MU).

RESUMEN / SUMMARY: - BACKGROUND: The AGO-ETC trial compared 5-year relapse-free survival of intense dose-dense (IDD) sequential chemotherapy with epirubicin (E), paclitaxel (T), and cyclophosphamide © (IDD-ETC) every 2 weeks vs conventional scheduled epirubicin/cyclophosphamide followed by paclitaxel (EC-->T) (every 3 weeks) as adjuvant treatment in high-risk breast cancer patients. The objective of this study was to evaluate the safety and efficacy of epoetin alfa in a second randomization of the intense dose-dense arm. METHODS: One thousand two hundred eighty-four patients were enrolled; 658 patients were randomly assigned to the IDD-ETC treatment group. Within the IDD-ETC group, 324 patients were further randomly assigned to the epoetin alfa group, and 319 were randomly assigned to the non-erythropoiesis-stimulating agent (ESA) control group. Primary efficacy endpoints included change in hemoglobin level from baseline to Cycle 9 and the percentage of subjects requiring red blood cell transfusion. Relapse-free survival, overall survival, and intramammary relapse were secondary endpoints estimated with Kaplan-Meier and Cox regression methods. Except for the primary hypothesis, all statistical tests were two-sided. RESULTS: Epoetin alfa avoided the decrease in hemoglobin level (no decrease in the epoetin alfa group vs - 2.20g/dL change for the control group; $P < .001$) and statistically significantly reduced the percentage of subjects requiring red blood cell transfusion (12.8% vs 28.1%; $P < .0001$). The incidence of thrombotic events was 7% in the epoetin alfa arm vs 3% in the control arm. After a median follow-up of 62 months, epoetin alfa treatment did not affect overall survival, relapse-free survival, or intramammary relapse. CONCLUSIONS: Epoetin alfa resulted in improved hemoglobin levels and decreased transfusions without an impact on relapse-free or overall survival. However, epoetin alfa had an adverse effect, resulting in increased thrombosis.

TÍTULO / TITLE: - Nivolumab plus ipilimumab in advanced melanoma.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jul 11;369(2):122-33. doi: 10.1056/NEJMoa1302369. Epub 2013 Jun 2.

●● [Enlace al texto completo \(gratis o de pago\) 1056/NEJMoa1302369](#)

AUTORES / AUTHORS: - Wolchok JD; Kluger H; Callahan MK; Postow MA; Rizvi NA; Lesokhin AM; Segal NH; Ariyan CE; Gordon RA; Reed K; Burke MM; Caldwell A; Kronenberg SA; Agunwamba BU; Zhang X; Lowy I; Inzunza HD; Feely W; Horak CE; Hong Q; Korman AJ; Wigginton JM; Gupta A; Sznol M

INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA. wolchokj@mskcc.org

RESUMEN / SUMMARY: - BACKGROUND: In patients with melanoma, ipilimumab (an antibody against cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) prolongs overall survival, and nivolumab (an antibody against the programmed death 1 [PD-1] receptor) produced durable tumor regression in a phase 1 trial. On the basis of their distinct immunologic mechanisms of action and supportive preclinical data, we conducted a phase 1 trial of nivolumab combined with ipilimumab in patients with advanced melanoma. METHODS: We administered intravenous doses of nivolumab and ipilimumab in patients every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. RESULTS: A total of 53 patients received concurrent therapy with nivolumab and ipilimumab, and 33 received sequenced treatment. The objective-response rate (according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥ 24 weeks) was observed in 65% of patients. At the maximum doses that were associated with an acceptable level of adverse events (nivolumab at a dose of 1 mg per kilogram of body weight and ipilimumab at a dose of 3 mg per kilogram), 53% of patients had an objective response, all with tumor reduction of 80% or more. Grade 3 or 4 adverse events related to therapy occurred in 53% of patients in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among patients in the sequenced-regimen group, 18% had grade 3 or 4 adverse events related to therapy and the objective-response rate was 20%. CONCLUSIONS: Concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and provided clinical activity that appears to be distinct from that in published data on monotherapy, with rapid and deep tumor regression in a substantial proportion of patients. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; ClinicalTrials.gov number, NCT01024231.)

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/adverse effects\$!"25.90\$!" &&CLCL&& &&THTH&& /*therapeutic
use

[9]

TÍTULO / TITLE: - Case records of the Massachusetts General Hospital. Case 21-2013. A 68-year-old man with metastatic melanoma.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jul 11;369(2):173-83. doi: 10.1056/NEJMcp1302332.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMcp1302332](#)

AUTORES / AUTHORS: - Sullivan RJ; Lawrence DP; Wargo JA; Oh KS; Gonzalez RG; Piris A

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Massachusetts General Hospital, Boston, USA.

[10]

TÍTULO / TITLE: - Soluble human epidermal growth factor receptor 2 (HER2) levels in patients with HER2-positive breast cancer receiving chemotherapy with or without trastuzumab: Results from North Central Cancer Treatment Group adjuvant trial N9831.

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

REVISTA / JOURNAL: - Cancer. 2013 Aug 1;119(15):2675-82. doi: 10.1002/cncr.28130. Epub 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28130](#)

AUTORES / AUTHORS: - Moreno-Aspitia A; Hillman DW; Dyar SH; Tenner KS; Gralow J; Kaufman PA; Davidson NE; Lafky JM; Reinholz MM; Lingle WL; Kutteh LA; Carney WP; Dueck AC; Perez EA

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Mayo Clinic, Jacksonville, Florida.

RESUMEN / SUMMARY: - BACKGROUND: Increased soluble human epidermal growth factor receptor 2 (sHER2) is an indicator of a poor prognosis in HER2-positive metastatic breast cancer. In this study, the authors evaluated levels of sHER2 during treatment and at the time of disease recurrence in the adjuvant North Central Cancer Treatment Group N9831 clinical trial. METHODS: The objectives were to describe sHER2 levels during treatment and at the time of recurrence in patients who were randomized to treatment arms A (standard chemotherapy), B (standard chemotherapy with sequential trastuzumab), and C (standard chemotherapy with concurrent trastuzumab). Baseline samples were available from 2318 patients, serial samples were available from 105 patients, and recurrence samples were available from 124 patients. The cutoff sHER2 value for the assay was 15 ng/mL. Statistical methods included repeated

measures linear models, Wilcoxon rank-sum tests, and Cox regression models. RESULTS: There were differences between groups in terms of age, menopausal status, and hormone receptor status. Within treatment arms A, B, and C, patients who had baseline sHER2 levels ≥ 15 ng/mL had worse disease-free survival than patients who had baseline sHER2 levels < 15 ng/mL (arm A: hazard ratio, 1.81; $P = .0014$; arm B: hazard ratio, 2.08; $P = .0015$; arm C: hazard ratio, 1.96; $P = .01$). Among the 124 patients who experienced disease recurrence, sHER2 levels increased from baseline to the time of recurrence in arms A and B but remained unchanged in arm C. Patients who had recurrence sHER2 levels ≥ 15 ng/mL had a shorter survival after recurrence with a 3-year overall survival rate of 51% compared with 77% for those who had recurrence sHER2 levels < 15 ng/mL (hazard ratio, 2.36; 95% confidence interval, 1.19-4.70; $P = .01$). CONCLUSIONS: In patients with early stage, HER2-positive breast cancer, a high baseline sHER2 level was identified as a prognostic marker associated with shorter disease-free survival, and a high sHER2 level at recurrence was predictive of shorter survival. Cancer 2013;119:2675-2682. © 2013 American Cancer Society.

[11]

TÍTULO / TITLE: - The predictive impact of body mass index on the efficacy of extended adjuvant endocrine treatment with anastrozole in postmenopausal patients with breast cancer: an analysis of the randomised ABCSG-6^a trial.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 6;109(3):589-96. doi: 10.1038/bjc.2013.367. Epub 2013 Jul 18.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.367](#)

AUTORES / AUTHORS: - Gnant M; Pfeiler G; Stoger H; Mlineritsch B; Fitzal F; Balic M; Kwasny W; Seifert M; Stierer M; Dubsy P; Greil R; Steger G; Samonigg H; Fesl C; Jakesz R

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - Background: We investigated whether body mass index (BMI) can be used as a predictive parameter indicating patients who benefit from extended aromatase inhibitor (AI) treatment. Methods: The ABCSG-6^a trial re-randomised event-free postmenopausal hormone receptor-positive patients from the ABCSG-6 trial to receive either 3 additional years of endocrine therapy using anastrozole vs nil. In this retrospective analysis, we investigated the prognostic and predictive impact of BMI on disease outcome and safety. Results: In all, 634 patients (177 normal weight, 307 overweight, and 150 obese) patients were included in this analysis. Normal weight patients with additional 3 years of anastrozole halved their risk of disease recurrence (disease-free survival (DFS) HR 0.48; $P=0.02$) and death (HR 0.45; $P=0.06$) and had only a fifth of the risk of distant metastases (HR 0.22; $P=0.05$)

compared with normal weight patients without any further treatment. In contrast, overweight+obese patients derived no benefit from additional 3 years of anastrozole (DFS HR 0.93; P=0.68; distant recurrence-free survival HR 0.91; P=0.78; and OS HR 0.9; P=0.68). The possible predictive impact of BMI on extended endocrine treatment could be strengthened by a Cox regression interaction model between BMI and treatment (P=0.07). Conclusion: Body mass index may be used to predict outcome benefit of extended AI treatment in patients with receptor-positive breast cancer.

[12]

TÍTULO / TITLE: - Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma.

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

REVISTA / JOURNAL: - N Engl J Med. 2013 Jul 11;369(2):134-44. doi: 10.1056/NEJMoa1305133. Epub 2013 Jun 2.

●● Enlace al texto completo (gratis o de pago) [1056/NEJMoa1305133](#)

AUTORES / AUTHORS: - Hamid O; Robert C; Daud A; Hodi FS; Hwu WJ; Kefford R; Wolchok JD; Hersey P; Joseph RW; Weber JS; Dronca R; Gangadhar TC; Patnaik A; Zarour H; Joshua AM; Gergich K; Ellassaiss-Schaap J; Algazi A; Mateus C; Boasberg P; Tumei PC; Chmielowski B; Ebbinghaus SW; Li XN; Kang SP; Ribas A

INSTITUCIÓN / INSTITUTION: - Angeles Clinic and Research Institute, Los Angeles, CA, USA.

RESUMEN / SUMMARY: - BACKGROUND: The programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer. We tested the anti-PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma. METHODS: We administered lambrolizumab intravenously at a dose of 10 mg per kilogram of body weight every 2 or 3 weeks or 2 mg per kilogram every 3 weeks in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not. Tumor responses were assessed every 12 weeks. RESULTS: A total of 135 patients with advanced melanoma were treated. Common adverse events attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the adverse events were low grade. The confirmed response rate across all dose cohorts, evaluated by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between patients who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the

majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival among the 135 patients was longer than 7 months. CONCLUSIONS: In patients with advanced melanoma, including those who had had disease progression while they had been receiving ipilimumab, treatment with lambrolizumab resulted in a high rate of sustained tumor regression, with mainly grade 1 or 2 toxic effects. (Funded by Merck Sharp and Dohme; ClinicalTrials.gov number, NCT01295827.).

[13]

TÍTULO / TITLE: - Clinical effects of A4889G and T6235C polymorphisms in cytochrome P-450 CYP1A1 for breast cancer patients treated with tamoxifen: implications for tumor aggressiveness and patient survival.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Jul 11.

- Enlace al texto completo (gratis o de pago) [1007/s00280-013-2221-](#)

[y](#)

AUTORES / AUTHORS: - Cardoso-Filho C; Sarian LO; de Oliveira CB; da Silveira Bossi L; Lourenco GJ; Lima CS; Gurgel MS

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Campinas State University, Campinas, Sao Paulo, Brazil, ccf@unicamp.br.

RESUMEN / SUMMARY: - PURPOSE: Individual differences in cytochrome P-450 efficiency partly explain their variations in resistance to tamoxifen and estrogen metabolism. Two polymorphisms of the CYP1A1 gene-A4889G and T6235C-are known to affect activation of estrone and estradiol and to deregulate concentration of highly active tamoxifen metabolites. However, the clinicopathologic implications of these findings have not yet been evaluated. OBJECTIVE: The objective of this study is to evaluate whether T6235C and A4889G gene polymorphisms are related to pathological presentations and clinical outcomes of ER+/PR+ breast cancer (BC) in women using tamoxifen. METHODS: We included 405 women with ER+/PR+ tumors, who used tamoxifen as their primary therapy, and for whom 5-year follow-up data were available. We evaluated associations within clinicopathologic features, including overall 5-year survival, with CYP1A1 gene status. RESULTS: Univariate analysis showed that a slightly higher proportion of women with AG/GG genotypes were of European descent (P = 0.05) and that TC/CC genotype was significantly associated with premenopausal status (P = 0.01); however, no significant association remained after multivariate adjustment. Women with CYP1A1 genotypes other than AA and TT were more prone to develop low-grade tumors; 85.9 % of tumors in AA and TT genotype groups were grade III, but only 76.1 % of tumors in carriers of the polymorphisms were grade III (adjusted P = 0.02; OR 0.51 for grade III disease; 95 % CI 0.28-0.93). After 60

months of follow-up, ~75 % of the women were alive. There was no significant difference in survival related to the CYP1A1 gene status. CONCLUSIONS: Breast cancer patients carrying CYP1A1 gene polymorphisms developed less aggressive tumors, but showed no evidence of better prognoses.

[14]

TÍTULO / TITLE: - Engineered SIRPalpha variants as immunotherapeutic adjuvants to anticancer antibodies.

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

REVISTA / JOURNAL: - Science. 2013 Jul 5;341(6141):88-91. doi: 10.1126/science.1238856. Epub 2013 May 30.

●● Enlace al texto completo (gratis o de pago) 1126/science.1238856

AUTORES / AUTHORS: - Weiskopf K; Ring AM; Ho CC; Volkmer JP; Levin AM; Volkmer AK; Ozkan E; Fernhoff NB; van de Rijn M; Weissman IL; Garcia KC

INSTITUCIÓN / INSTITUTION: - Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA.

RESUMEN / SUMMARY: - CD47 is an antiphagocytic signal that cancer cells employ to inhibit macrophage-mediated destruction. Here, we modified the binding domain of human SIRPalpha, the receptor for CD47, for use as a CD47 antagonist. We engineered high-affinity SIRPalpha variants with about a 50,000-fold increased affinity for human CD47 relative to wild-type SIRPalpha. As high-affinity SIRPalpha monomers, they potently antagonized CD47 on cancer cells but did not induce macrophage phagocytosis on their own. Instead, they exhibited remarkable synergy with all tumor-specific monoclonal antibodies tested by increasing phagocytosis in vitro and enhancing antitumor responses in vivo. This “one-two punch” directs immune responses against tumor cells while lowering the threshold for macrophage activation, thereby providing a universal method for augmenting the efficacy of therapeutic anticancer antibodies.

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&&BABABA&& &&CECECE&& &&PHPHPH&& &&ETETET&&

/*immunology

[15]

TÍTULO / TITLE: - First line treatment with rituximab- Hyper-CVAD alternating with rituximab- Methotrexate- Cytarabine and followed by consolidation with 90Y-Ibritumomab-Tiuxetan in patients with mantle cell lymphoma. Results of a phase 2 pilot multicenter trial from the GELTAMO group.

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

REVISTA / JOURNAL: - Haematologica. 2013 Jun 10.

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

3324/haematol.2013.088377

AUTORES / AUTHORS: - Arranz R; Garcia-Noblejas A; Grande C; Cannata-Ortiz J; Sanchez JJ; Garcia-Marco JA; Alaez C; Perez-Calvo J; Martinez-Sanchez P; Sanchez-Gonzalez B; Canales MA; Conde E; Martin A; Arranz E; Terol MJ; Salar A; Caballero D

INSTITUCIÓN / INSTITUTION: - Madrid, España;

RESUMEN / SUMMARY: - The prognosis for fit patients with mantle cell lymphoma has improved with intensive strategies. Currently, the role of maintenance/consolidation approaches is being tested as relapses continue appearing. In this trial we evaluated the feasibility, safety and efficacy of R-Hyper-CVAD alternating with R-MtxAraC followed by consolidation with 90Y-Ibritumomab-Tiuxetan. Patients received 6 cycles followed by a single dose of 90Y-Ibritumomab-Tiuxetan. Thirty patients were enrolled. Median age was 59 years. Twenty four patients finished the induction treatment, 23 achieved complete remission (77%, 95% confidence interval 60-93) and one patient had progressive disease (3%). Eighteen patients (60%), all in complete remission, received consolidation. In the intent- to- treat population, failure free, progression free and overall survival at 4 years were 40 % (95% confidence interval 20.4-59.6), 52% (95% confidence interval 32.4-71.6) and 81% (95% confidence interval 67.28-94.72), respectively. For patients who received consolidation, failure free and overall survival were 55% (95% confidence interval 31.48-78.52) and 87% (95% confidence interval 70-100), respectively. Hematological toxicity was significant during induction and responsible for one death (3.3%). After consolidation, grade 3-4 neutropenia and thrombocytopenia were observed in 72% and 83% of patients, with median duration of 5 and 12 weeks, respectively. Six (20%) patients died, 3 due to secondary malignancies (myelodysplastic syndrome and bladder and rectum carcinomas). In conclusion, our experience with R-Hyper-CVAD/R-MtxAraC followed by consolidation with 90Y-Ibritumomab-Tiuxetan is efficacious although less feasible than expected. The unacceptable toxicity observed, specially secondary malignancies, advise against the indication of this strategy. Trial registration: clinical.gov identifier: NCT2005-004400-37.

[16]

TÍTULO / TITLE: - Serum Androgens As Prognostic Biomarkers in Castration-Resistant Prostate Cancer: Results From an Analysis of a Randomized Phase III Trial.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 1;31(22):2791-8. doi: 10.1200/JCO.2012.45.4595. Epub 2013 Jul 1.

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

[1200/JCO.2012.45.4595](#)

AUTORES / AUTHORS: - Ryan CJ; Molina A; Li J; Kheoh T; Small EJ; Haqq CM; Grant RP; de Bono JS; Scher HI

INSTITUCIÓN / INSTITUTION: - University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero St, San Francisco, CA 94115; ryanc@medicine.ucsf.edu.

RESUMEN / SUMMARY: - **PURPOSE** In the phase III study COU-AA-301, abiraterone acetate (AA) plus prednisone (P) prolonged overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel administration. In this article, we investigate the relationship between baseline serum androgen (SA) levels and OS. **PATIENTS AND METHODS** COU-AA-301 is a randomized, double-blind study of AA (1,000 mg every day) plus P (5 mg by mouth twice daily; n = 797) versus P alone (n = 398). Randomization was stratified by Eastern Cooperative Oncology Group performance status (0 to 1 v 2), pain (Brief Pain Inventory-Short Form over past 24 hours: 4 to 10, present; v 0 to 3, absent), prior chemotherapy (1 v 2), and progression (prostate-specific antigen v radiographic). Association of baseline SA (testosterone, androstenedione, dehydroepiandrosterone sulfate), was measured by ultrasensitive liquid-liquid extraction or protein precipitation and two-dimensional liquid chromatography coupled to mass spectrometry, with OS determined by bivariate and multivariable Cox models. OS was examined with SA as greater than median and less than or equal to the median. Results Median survival increased with each quartile increase in testosterone level regardless of treatment arm. SA levels at baseline strongly associated with survival (P < .0001) in bivariate and multivariable analyses. Longer survival was observed for patients with SA above median compared with below median in both the AA and P arms (eg, testosterone, AA; hazard ratio, 0.64; 95% CI, 0.53 to 0.77; P < .0001). Treatment with AA led to longer survival versus P alone in the above- or below-median group for all androgens. **CONCLUSION** SA, measured with a novel ultrasensitive assay in COU-AA-301, is prognostic for OS and may be useful for risk stratification in mCRPC clinical trials.

[17]

TÍTULO / TITLE: - MDM2 promoter polymorphism and p53 codon 72 polymorphism in chronic myeloid leukemia: The association between MDM2 promoter genotype and disease susceptibility, age of onset, and blast-free survival in chronic phase patients receiving imatinib.

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

REVISTA / JOURNAL: - Mol Carcinog. 2013 Jul 2. doi: 10.1002/mc.22061.

●● Enlace al texto completo (gratis o de pago) [1002/mc.22061](#)

AUTORES / AUTHORS: - Liu YC; Hsiao HH; Yang WC; Liu TC; Chang CS; Yang MY; Lin PM; Hsu JF; Lee CP; Lin SF

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; Department of Internal Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; Graduate Institute of

Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - The genetic or functional inactivation of the p53 pathway plays an important role with regards to disease progression from the chronic phase (CP) to blast phase (BP) and imatinib treatment response in chronic myeloid leukemia (CML). Two functional single nucleotide polymorphisms (SNPs), p53 R72P and MDM2 SNP309, are associated with alternation of p53 activity, however the association regarding CML susceptibility and BP transformation under imatinib treatment is unclear. The MDM2 SNP309 genotype was determined by polymerase chain reaction-restriction fragment length polymorphism and confirmed by direct sequencing from 116 CML patients, including 104 in the CP at diagnosis, and 162 healthy Taiwanese controls. The p53 R72P polymorphism was examined in all CML patients. The SNP309 G/G genotype was associated with an increased risk of CML susceptibility (OR: 1.82, 95% CI: 1.03-3.22, P = 0.037), and an earlier age of disease onset (log-rank P = 0.005) compared with the T/T + T/G genotypes. Higher MDM2 mRNA expression was found in G/G genotype compared with T/T (P = 0.034) and T/T + T/G (P = 0.056) genotypes. No associations were found between the p53 R72P genotypes and clinical parameters and survival outcomes. Among 62 CP patients receiving imatinib as first-line therapy, the G/G genotype was associated with a shorter blast-free survival (log-rank P = 0.048) and more clonal evolution compared with the T/T + T/G genotypes. In patients with advanced diseases at diagnosis, the G/G genotype was associated with a poor overall survival (log-rank P = 0.006). Closely monitoring CML patients harboring the G/G genotype and further large-scale studies are warranted. © 2013 Wiley Periodicals, Inc.

[18]

TÍTULO / TITLE: - Does thyroid-stimulating hormone influence the prognosis of patients with endometrial cancer? A multicentre trial.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 9;109(1):215-8. doi: 10.1038/bjc.2013.282. Epub 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.282](#)

AUTORES / AUTHORS: - Seebacher V; Hofstetter G; Polterauer S; Reinthaller A; Grimm C; Schwameis R; Taucher S; Wagener A; Marth C; Concin N

INSTITUCIÓN / INSTITUTION: - Department of Gynaecology and Gynaecological Oncology, Comprehensive Cancer Centre Vienna, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.

RESUMEN / SUMMARY: - Background: Thyroid function has been suggested to interfere with tumour biology and prognosis in different cancers. The present study was performed to investigate the impact of pre-therapeutic serum thyroid-stimulating hormone (TSH) levels on the prognosis of patients with endometrial

cancer. Methods: Pre-therapeutic serum TSH was investigated in 199 patients with endometrial cancer. After stratification in TSH risk groups, univariate and multivariable survival analyses were performed. Results: Elevated TSH was independently associated with poor disease-specific survival in univariate/multivariable survival analyses ($P=0.01$ and $P=0.03$, respectively). Conclusion: Thyroid-stimulating hormone may serve as a novel and independent prognostic parameter for disease-specific survival in patients with endometrial cancer.

[19]

TÍTULO / TITLE: - Detection of MRD may predict the outcome of patients with Philadelphia-chromosome positive ALL treated with tyrosine kinase inhibitors plus chemotherapy.

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

REVISTA / JOURNAL: - Blood. 2013 Jul 8.

●● [Enlace al texto completo \(gratis o de pago\) 1182/blood-2012-11-466482](#)

AUTORES / AUTHORS: - Ravandi F; Jorgensen JL; Thomas DA; O'Brien S; Garris R; Faderl S; Huang X; Wen S; Burger JA; Ferrajoli A; Kebriaei P; Champlin RE; Estrov Z; Challagundla P; Wang SA; Luthra R; Cortes JE; Kantarjian HM

INSTITUCIÓN / INSTITUTION: - Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States;

RESUMEN / SUMMARY: - From April 2001 to March 2011, 122 patients with newly diagnosed Ph+ ALL were treated with hyperCVAD + imatinib ($n=54$) and hyperCVAD + dasatinib ($n=68$). 115 (94%) achieved CR including 101 patients who achieved it with only one induction course and had at least one minimal residual disease (MRD) assessment; 25 patients underwent an allogeneic stem cell transplant in first CR and were excluded, leaving 76 patients as the subject of this report. MRD monitoring by multi-parameter flow cytometry (MFC) and quantitative polymerase chain reaction (RQ-PCR) was performed at the end of induction and at approximately 3 month intervals thereafter. Median age for the 76 patients was 54 years (range, 21 - 84 years). There was no difference in survival by achievement of at least a major molecular response (MMR, BCR-ABL/ABL $< 0.1\%$) at CR ($p=0.22$). Patients achieving MMR at 3, 6, 9, and 12 months had a significantly better survival ($p=0.02$, $p=0.04$, and $p=0.05$, and $p=0.01$, respectively). Achievement of negative MFC at CR did not predict for improved survival ($p=0.2$). At 3 and 12 months, negative MRD by MFC was associated with improved survival ($p=0.04$ and $p=0.001$). MRD monitoring by PCR and MFC identifies patients who benefit from treatment intensification in first CR. (Registered at clinicaltrials.gov: NCT00390793).

[20]

TÍTULO / TITLE: - Usefulness of bone turnover markers as predictors of mortality risk, disease progression and skeletal-related events appearance in patients with prostate cancer with bone metastases following treatment with zoledronic acid: TUGAMO study.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jun 25;108(12):2565-72. doi: 10.1038/bjc.2013.270. Epub 2013 May 30.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.270](#)

AUTORES / AUTHORS: - de la Piedra C; Alcaraz A; Bellmunt J; Meseguer C; Gomez-Caamano A; Ribal MJ; Vazquez F; Anido U; Samper P; Esteban E; Alvarez-Ossorio JL; Lara PC; San Jose LA; Contreras JA; Del Alba AG; Gonzalez-Gragera B; Tabernero AJ; Gonzalez-Enguita C; Fernandez JM; Garcia-Escudero A; Gomez-Veiga F; Mendez MJ; Segarra J; Virizuela JA; Carles J; Lassa A; Calderero V; Constela M; Delgado D; Manas A; Murias A; Reynes G; Rodriguez B; Rubio G; Sanchez E; Unda M; Solsona E; Martinez-Javaloyas JM; Comet-Batlle J; Quicios C; Martin-Fernandez M; Mahillo-Fernandez I; Morote J

INSTITUCIÓN / INSTITUTION: - Bioquímica Investigación, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, Madrid, España.

RESUMEN / SUMMARY: - Background:Owing to the limited validity of clinical data on the treatment of prostate cancer (PCa) and bone metastases, biochemical markers are a promising tool for predicting survival, disease progression and skeletal-related events (SREs) in these patients. The aim of this study was to evaluate the predictive capacity of biochemical markers of bone turnover for mortality risk, disease progression and SREs in patients with PCa and bone metastases undergoing treatment with zoledronic acid (ZA).Methods:This was an observational, prospective and multicenter study in which ninety-eight patients were included. Patients were treated with ZA (4 mg every 4 weeks for 18 months). Data were collected at baseline and 3, 6, 9, 12, 15 and 18 months after the beginning of treatment. Serum levels of bone alkaline phosphatase (BALP), aminoterminal propeptide of procollagen type I (P1NP) and beta-isomer of carboxiterminal telopeptide of collagen I (beta-CTX) were analysed at all points in the study. Data on disease progression, SREs development and survival were recorded.Results:Cox regression models with clinical data and bone markers showed that the levels of the three markers studied were predictive of survival time, with beta-CTX being especially powerful, in which a lack of normalisation in visit 1 (3 months after the beginning of treatment) showed a 6.3-times more risk for death than in normalised patients. Levels of these markers were also predictive for SREs, although in this case BALP and P1NP proved to be better predictors. We did not find any relationship between bone markers and disease progression.Conclusion:In patients with PCa and bone metastases treated with ZA, beta-CTX and P1NP can be considered suitable predictors for mortality risk, while BALP and P1NP are appropriate for

SREs. The levels of these biomarkers 3 months after the beginning of treatment are especially important.

[21]

TÍTULO / TITLE: - Tyrosine Kinase Inhibitor Therapy Induces Remission in a Patient With Refractory EBF1-PDGFRB-Positive Acute Lymphoblastic Leukemia.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 8.

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

[1200/JCO.2012.47.6770](#)

AUTORES / AUTHORS: - Weston BW; Hayden MA; Roberts KG; Bowyer S; Hsu J; Fedoriw G; Rao KW; Mullighan CG

INSTITUCIÓN / INSTITUTION: - The University of North Carolina, Chapel Hill, NC.

[22]

TÍTULO / TITLE: - New hematologic response criteria predict survival in patients with immunoglobulin light chain amyloidosis treated with high-dose melphalan and autologous stem-cell transplantation.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 20;31(21):2749-50. doi: 10.1200/JCO.2013.48.7736. Epub 2013 Jun 17.

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

[1200/JCO.2013.48.7736](#)

AUTORES / AUTHORS: - Girnius S; Seldin DC; Cibeira MT; Sanchorawala V

INSTITUCIÓN / INSTITUTION: - Boston Medical Center, 820 Harrison Ave, FGH Building 1007, Boston, MA 02118; Vaishali.Sanchorawala@bmc.org.

[23]

TÍTULO / TITLE: - Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 6;109(3):582-8. doi: 10.1038/bjc.2013.324. Epub 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.324](#)

AUTORES / AUTHORS: - Yang H; Zong X; Yu Y; Shao G; Zhang L; Qian C; Bian Y; Xu X; Sun W; Meng X; Ding X; Chen D; Zou D; Xie S; Zheng Y; Zhang J; He X; Sun C; Yu X; Ni J

INSTITUCIÓN / INSTITUTION: - Department of Breast Surgery, Zhejiang Cancer Hospital, 38 Guangji Road, Hangzhou 310022, China.

RESUMEN / SUMMARY: - Background: This study is to investigate the effects of goserelin+tamoxifen (TAM) on estradiol level, breast density (BD), endometrial thickness (ET), and blood lipids in premenopausal and perimenopausal women with hormone receptor-positive early-stage breast cancer. Methods: This study recruited 110 premenopausal and perimenopausal patients with hormone receptor-positive early-stage breast cancer between 22 June 2008 and 31 December 2009 and randomly assigned them to receive either goserelin plus TAM or TAM alone for 1.5 years. Blood levels of sex hormones and lipids and ET were determined at 0, 3, 6, 12, and 18 months. Contralateral BD was also measured at 0, 12, and 18 months. Results: Five participants dropped out of the goserelin plus TAM group, and two participants dropped out of the TAM-alone group before initiation of endocrine therapy. The rest of patients received scheduled treatment and 3 years of median follow-up. No serious adverse effects were observed, and only two local recurrences have been observed in these patients. Estradiol level and BD were lower in the goserelin plus TAM group than in the TAM-alone group ($P < 0.05$). The endometrium in the goserelin plus TAM group was significantly thinner than that in the TAM-alone group ($P < 0.05$), and women in the TAM-alone group exhibited endometrial thickening over the course of the study. Furthermore, no significant differences in blood lipid levels were reported between the two groups. Conclusion: The data from the current study demonstrated that the addition of goserelin to TAM results in downregulation of estradiol level, followed by significant reduction in BD and ET in premenopausal and perimenopausal women with hormone receptor-positive breast cancer, which may eventually lead to better outcome in these patients.

[24]

TÍTULO / TITLE: - Randomized Phase II Study of the Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Cetuximab With Cisplatin Versus Cisplatin Alone in Patients With Metastatic Triple-Negative Breast Cancer.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 10;31(20):2586-92. doi: 10.1200/JCO.2012.46.2408. Epub 2013 Jun 3.

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

[1200/JCO.2012.46.2408](#)

AUTORES / AUTHORS: - Baselga J; Gomez P; Greil R; Braga S; Climent MA; Wardley AM; Kaufman B; Stemmer SM; Pego A; Chan A; Goeminne JC; Graas MP; Kennedy MJ; Ciruelos Gil EM; Schneeweiss A; Zobel A; Groos J; Melezinkova H; Awada A

INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; baselgaj@mskcc.org.

RESUMEN / SUMMARY: - PURPOSE Epidermal growth factor receptor is overexpressed in metastatic triple-negative breast cancers (mTNBCs), an aggressive subtype of breast cancer. Our randomized phase II study investigated cisplatin with or without cetuximab in this setting. PATIENTS AND METHODS Patients who had received no more than one previous chemotherapy regimen were randomly assigned on a 2:1 schedule to receive no more than six cycles of cisplatin plus cetuximab or cisplatin alone. Patients receiving cisplatin alone could switch to cisplatin plus cetuximab or cetuximab alone on disease progression. The primary end point was overall response rate (ORR). Secondary end points studied included progression-free survival (PFS), overall survival (OS), and safety profiles. Analyses included a significance level of alpha = .10 with no adjustments for multiplicity. Results The full analysis set comprised 115 patients receiving cisplatin plus cetuximab and 58 receiving cisplatin alone; 31 patients whose disease progressed on cisplatin alone switched to cetuximab-containing therapy. The ORR was 20% (95% CI, 13 to 29) with cisplatin plus cetuximab and 10% (95% CI, 4 to 21) with cisplatin alone (odds ratio, 2.13; 95% CI, 0.81 to 5.59; P = .11). Cisplatin plus cetuximab resulted in longer PFS compared with cisplatin alone (median, 3.7 v 1.5 months; hazard ratio [HR], 0.67; 95% CI, 0.47 to 0.97; P = .032). Corresponding median OS was 12.9 versus 9.4 months (HR, 0.82; 95% CI, 0.56 to 1.20; P = .31). Common grade $\frac{3}{4}$ adverse events included acne-like rash, neutropenia, and fatigue. CONCLUSION While the primary study end point was not met, adding cetuximab to cisplatin doubled the ORR and appeared to prolong PFS and OS, warranting further investigation in mTNBC.

[25]

TÍTULO / TITLE: - Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial.

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

REVISTA / JOURNAL: - Lancet Oncol. 2013 Jul 19. pii: S1470-2045(13)70310-3. doi: 10.1016/S1470-2045(13)70310-3.

●● Enlace al texto completo (gratis o de pago) [1016/S1470-2045\(13\)70310-3](#)

AUTORES / AUTHORS: - Garassino MC; Martelli O; Broggin M; Farina G; Veronese S; Rulli E; Bianchi F; Bettini A; Longo F; Moscetti L; Tomirotti M; Marabese M; Ganzinelli M; Lauricella C; Labianca R; Floriani I; Giaccone G; Torri V; Scanni A; Marsoni S

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Fatebenefratelli e Oftalmico Hospital, Milan, Italy; Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy.

RESUMEN / SUMMARY: - BACKGROUND: Erlotinib is registered for treatment of all patients with advanced non-small-cell lung cancer (NSCLC). However, its

efficacy for treatment of patients whose tumours are EGFR wild-type-which includes most patients-is still contentious. We assessed the efficacy of erlotinib compared with a standard second-line chemotherapy in such patients.

METHODS: We did this randomised controlled trial in 52 Italian hospitals. We enrolled patients who had metastatic NSCLC, had had platinum-based chemotherapy, and had wild-type EGFR as assessed by direct sequencing. Patients were randomly assigned centrally (1:1) to receive either erlotinib orally 150 mg/day or docetaxel intravenously 75 mg/m² every 21 days or 35 mg/m² on days 1, 8, and 15, every 28 days. Randomisation was stratified by centre, stage, type of first-line chemotherapy, and performance status. Patients and investigators who gave treatments or assessed outcomes were not masked to treatment allocation, investigators who analysed results were. The primary endpoint was overall survival in the intention-to-treat population. The study is registered at ClinicalTrials.gov, number NCT00637910. **FINDINGS:** We screened 702 patients, of whom we genotyped 540. 222 patients were enrolled (110 assigned to docetaxel vs 112 assigned to erlotinib). Median overall survival was 8.2 months (95% CI 5.8-10.9) with docetaxel versus 5.4 months (4.5-6.8) with erlotinib (adjusted hazard ratio [HR] 0.73, 95% CI 0.53-1.00; p=0.05). Progression-free survival was significantly better with docetaxel than with erlotinib: median progression-free survival was 2.9 months (95% CI 2.4-3.8) with docetaxel versus 2.4 months (2.1-2.6) with erlotinib (adjusted HR 0.71, 95% CI 0.53-0.95; p=0.02). The most common grade 3-4 toxic effects were: low absolute neutrophil count (21 [20%] of 104 in the docetaxel group vs none of 107 in the erlotinib group), skin toxic effects (none vs 15 [14%]), and asthenia (ten [10%] vs six [6%]). **INTERPRETATION:** Our results show that chemotherapy is more effective than erlotinib for second-line treatment for previously treated patients with NSCLC who have wild-type EGFR tumours. **FUNDING:** Agenzia Italiana del Farmaco.

[26]

TÍTULO / TITLE: - Phase II Randomized Trial Comparing High-dose Interferon Alfa-2b with Temozolomide plus Cisplatin as Systemic Adjuvant Therapy for Resected Mucosal Melanoma.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0739](#)

AUTORES / AUTHORS: - Lian B; Si L; Cui C; Chi Z; Sheng X; Mao L; Li S; Kong Y; Tang B; Guo J

INSTITUCIÓN / INSTITUTION: - Department of Renal cancer and Melanoma, Peking University Cancer Hospital & Institute.

RESUMEN / SUMMARY: - **PURPOSE:** Mucosal melanoma is rare and associated with extremely poor prognosis. However, standard adjuvant therapy for mucosal

melanoma has not been established. We conducted a randomized phase II clinical trial in resected mucosal melanoma (MM) patients to compare the efficacy and safety of high-dose IFN-alpha2b (HDI) and temozolomide-based chemotherapy as adjuvant therapy. EXPERIMENTAL DESIGN: MM patients in stage II/III after surgery were randomized into three groups: observation group (Group A, surgery alone), HDI group (Group B, treated with 15x10⁶ Unit/m²/day IFN-alpha2b, followed by 9x10⁶ Unit IFN-alpha2b), and temozolomide (200 mg/m²/day) plus cisplatin (75 mg/m²) group (Group C). The endpoints were relapse-free survival (RFS), overall survival (OS) and toxicities. RESULTS: 189 patients were enrolled and finally analyzed. With a median follow-up of 26.8 months, the median RFS were 5.4, 9.4 and 20.8 months for Group A, B and C, respectively. Estimated median OS for Group A, B and C were 21.2, 40.4 and 48.7 months, respectively. Patients treated with temozolomide plus cisplatin demonstrated significant improvements in RFS (P < 0.001) and OS (P < 0.01) than those treated with either HDI or surgery alone. Toxicities were generally mild to moderate. CONCLUSION: Both temozolomide-based chemotherapy and HDI are effective and safe as adjuvant therapies for resected MM as compared to observation alone. However, HDI tends to be less effective than temozolomide-based chemotherapy for resected MM patients in respect to RFS. The temozolomide plus cisplatin regimen might be a better choice for resected MM patients.

[27]

TÍTULO / TITLE: - KRAS as prognostic biomarker in metastatic colorectal cancer patients treated with bevacizumab: a pooled analysis of 12 published trials.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):650. doi: 10.1007/s12032-013-0650-4. Epub 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0650-](#)

[4](#)

AUTORES / AUTHORS: - Petrelli F; Coinu A; Cabiddu M; Ghilardi M; Barni S

INSTITUCIÓN / INSTITUTION: - Medical Oncology Unit, Oncology Department, Azienda Ospedaliera Treviglio, Piazzale Ospedale 1, 24047, Treviglio (BG), Italy, faupe@libero.it.

RESUMEN / SUMMARY: - The significance of KRAS in advanced colorectal cancer (CRC) treated with bevacizumab (B) is not well understood. We conducted a systematic review and pooled analysis of published trials with the aim to assess the predictive and prognostic role of KRAS status in patients treated with B. We performed a systematic search of PubMed, EMBASE, Web of Science, and Cochrane Register of Controlled Trials. The primary endpoints included objective response rate (RR), progression-free survival (PFS), and overall survival (OS). The odds ratio (OR) for RR and hazard ratios (HRs) were calculated or extracted by published data either using a fixed effect model or a

random effect model. A total of 12 studies were included. A total of 2,266 patients were analysed (54 % were KRAS wt). The pooled RRs for KRAS wild-type (wt) versus mutated (mut) patients were 54.8 and 48.3 %, respectively (OR 1.42, P = 0.02). Median PFS was significantly longer in KRAS wt patients compared with that in KRAS mut patients (HR = 0.85; 95 % confidence interval (CI) 0.74-0.98; P = 0.02). Similarly, median OS was significantly better in wt KRAS patients compared with that in mut KRAS patients (HR = 0.65; 95 % CI 0.46-0.92; P = 0.01). This pooled analysis of 12 published studies shows that KRAS wt status is a good prognostic factor for B-based chemotherapy. Also, KRAS wt CRC is associated with a better RR with B plus chemotherapy than mut counterpart.

[28]

TÍTULO / TITLE: - Epidermal growth factor receptor expression as prognostic marker in patients with anal carcinoma treated with concurrent chemoradiation therapy.

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

REVISTA / JOURNAL: - Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):901-7. doi: 10.1016/j.ijrobp.2013.03.039. Epub 2013 Jun 5.

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

1016/j.ijrobp.2013.03.039

AUTORES / AUTHORS: - Fraunholz I; Rodel F; Kohler D; Diallo-Georgiopoulou M; Distel L; Falk S; Rodel C

INSTITUCIÓN / INSTITUTION: - Department of Radiotherapy and Oncology, Goethe University, Frankfurt/Main, Germany. Electronic address: inge.fraunholz@kgu.de.

RESUMEN / SUMMARY: - **PURPOSE:** To investigate the prognostic value of epidermal growth factor receptor (EGFR) expression in pretreatment tumor biopsy specimens of patients with anal cancer treated with concurrent 5-fluorouracil and mitomycin C-based chemoradiation therapy (CRT). **METHODS AND MATERIALS:** Immunohistochemical staining for EGFR was performed in pretreatment biopsy specimens of 103 patients with anal carcinoma. EGFR expression was correlated with clinical and histopathologic characteristics and with clinical endpoints, including local failure-free survival (LFFS), colostomy-free survival (CFS), distant metastases-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS). **RESULTS:** EGFR staining intensity was absent in 3%, weak in 23%, intermediate in 36% and intense in 38% of the patients. In univariate analysis, the level of EGFR staining was significantly correlated with CSS (absent/weak vs intermediate/intense expression: 5-year CSS, 70% vs 86%, P=.03). As a trend, this was also observed for DMFS (70% vs 86%, P=.06) and LFFS (70% vs 87%, P=.16). In multivariate analysis, N stage, tumor differentiation, and patients' sex were independent prognostic factors for CSS, whereas EGFR expression only reached borderline

significance (hazard ratio 2.75; P=.08). CONCLUSION: Our results suggest that elevated levels of pretreatment EGFR expression could be correlated with favorable clinical outcome in anal cancer patients treated with CRT. Further studies are warranted to elucidate how EGFR is involved in the response to CRT.

[29]

TÍTULO / TITLE: - Symptom Control and Quality of Life in LUX-Lung 3: A Phase III Study of Afatinib or Cisplatin/Pemetrexed in Patients With Advanced Lung Adenocarcinoma With EGFR Mutations.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 1.

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

[1200/JCO.2012.46.1764](#)

AUTORES / AUTHORS: - Yang JC; Hirsh V; Schuler M; Yamamoto N; O'Byrne KJ; Mok TS; Zazulina V; Shahidi M; Lungershausen J; Massey D; Palmer M; Sequist LV

INSTITUCIÓN / INSTITUTION: - James Chih-Hsin Yang, National Taiwan University Hospital, Taipei, Taiwan; Vera Hirsh, McGill University, Montreal, Quebec, Canada; Martin Schuler, West German Cancer Center, University Duisburg-Essen, Essen; Juliane Lungershausen, Boehringer Ingelheim GmbH, Ingelheim, Germany; Nobuyuki Yamamoto, Shizuoka Cancer Center, Shizuoka, Japan; Kenneth J. O'Byrne, St James' Hospital, Dublin, Ireland; Tony S.K. Mok, State Key Laboratory of Southern China, Hong Kong Cancer Institute, The Chinese University of Hong Kong, Hong Kong; Victoria Zazulina, Mehdi Shahidi, and Dan Massey, Boehringer Ingelheim Limited, Bracknell; Michael Palmer, Keele University, Keele, United Kingdom; and Lecia V. Sequist, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

RESUMEN / SUMMARY: - PURPOSE Patient-reported symptoms and health-related quality of life (QoL) benefits were investigated in a randomized, phase III trial of afatinib or cisplatin/pemetrexed. PATIENTS AND METHODS Three hundred forty-five patients with advanced epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma were randomly assigned 2:1 to afatinib 40 mg per day or up to six cycles of cisplatin/pemetrexed. Lung cancer symptoms and health-related QoL were assessed every 21 days until progression using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer-13 questionnaires. Analyses of cough, dyspnea, and pain were preplanned, including percentage of patients who improved on therapy, time to deterioration of symptoms, and change in symptoms over time. Results Questionnaire compliance was high. Compared with chemotherapy, afatinib significantly delayed the time to deterioration for cough (hazard ratio [HR], 0.60; 95% CI, 0.41 to 0.87; P = .007) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; P = .015), but not pain (HR, 0.83;

95% CI, 0.62 to 1.10; P = .19). More patients on afatinib (64%) versus chemotherapy (50%) experienced improvements in dyspnea scores (P = .010). Differences in mean scores over time significantly favored afatinib over chemotherapy for cough (P < .001) and dyspnea (P < .001). Afatinib showed significantly better mean scores over time in global health status/QoL (P = .015) and physical (P < .001), role (P = .004), and cognitive (P = .007) functioning compared with chemotherapy. Fatigue and nausea were worse with chemotherapy, whereas diarrhea, dysphagia, and sore mouth were worse with afatinib (all P < .01). CONCLUSION In patients with lung adenocarcinoma with EGFR mutations, first-line afatinib was associated with better control of cough and dyspnea compared with chemotherapy, although diarrhea, dysphagia, and sore mouth were worse. Global health status/QoL was also improved over time with afatinib compared with chemotherapy.

[30]

TÍTULO / TITLE: - Associations Between Genetic Polymorphisms of Epidermal Growth Factor Receptor (EGFR) and Survival of Colorectal Cancer (CRC) Patients Treated with 5-Fluorouracil-Based Chemotherapy.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3069-](#)

[4](#)

AUTORES / AUTHORS: - Lai CY; Sung FC; Hsieh LL; Tang R; Chiou HY; Wu FY; Yeh CC

INSTITUCIÓN / INSTITUTION: - Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan.

RESUMEN / SUMMARY: - PURPOSE: This retrospective cohort study investigated the association between epidermal growth factor receptor (EGFR) polymorphisms and clinical outcomes in colorectal cancer (CRC) patients treated with 5-fluorouracil (5-FU)-based chemotherapy. METHODS: We genotyped 3 EGFR polymorphisms including R497K, G-216T, and the (CA)_n repeat, among 499 histologically confirmed CRC patients who had received 5-FU-based chemotherapy after surgery between 1995 and 2001. Survival analyses of EGFR polymorphisms were performed by the log rank test and Kaplan-Meier curves. We used the Cox proportional hazard model to evaluate the association between EGFR genotypes and clinical outcomes. Stratification analysis by gender, tumor stage, and subsite were also carried out. RESULTS: CRC patients with the EGFR (CA)_n L/L genotype compared to those with the S/S+S/L genotype had a significantly better overall survival (L, ≥20 repeats; S, <20 repeats) (hazard ratio (HR) 0.74; 95 % confidence interval (CI) 0.57-0.95), particularly for patients who were male (HR 0.63; 95 % CI 0.44-0.90), who had stage IV disease (HR 0.70; 95 % CI 0.49-0.99), and who had rectal cancer (HR 0.62; 95 % CI 0.42-0.92). Better survival was prominent among

patients with the combined genotypes of EGFR (CA)n L/L, G-216T G/G, and R497K K/K (HR 0.51; 95 % CI 0.30-0.87), compared to those with the most common genotypes of the EGFR (CA)n S allele, G-216T G/G, and R497K R allele. CONCLUSIONS: EGFR polymorphisms can serve as prognostic predictors for CRC patients receiving 5-FU-based chemotherapy.

[31]

TÍTULO / TITLE: - Synthesis, Structure-Activity Relationships, and in Vivo Efficacy of the Novel Potent and Selective Anaplastic Lymphoma Kinase (ALK) Inhibitor 5-Chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) Currently in Phase 1 and Phase 2 Clinical Trials.

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

REVISTA / JOURNAL: - J Med Chem. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) 1021/jm400402g

AUTORES / AUTHORS: - Marsilje TH; Pei W; Chen B; Lu W; Uno T; Jin Y; Jiang T; Kim S; Li N; Warmuth M; Sarkisova Y; Sun F; Steffy A; Pferdekamper AC; Li AG; Joseph SB; Kim Y; Liu B; Tuntland T; Cui X; Gray NS; Steensma R; Wan Y; Jiang J; Chopiuk G; Li J; Gordon WP; Richmond W; Johnson K; Chang J; Groessl T; He YQ; Phimister A; Aycinena A; Lee CC; Bursulaya B; Karanewsky DS; Seidel HM; Harris JL; Michellys PY

INSTITUCIÓN / INSTITUTION: - Genomics Institute of the Novartis Research Foundation , 10675 John Jay Hopkins Drive, San Diego, California 92121, United States.

RESUMEN / SUMMARY: - The synthesis, preclinical profile, and in vivo efficacy in rat xenograft models of the novel and selective anaplastic lymphoma kinase inhibitor 15b (LDK378) are described. In this initial report, preliminary structure-activity relationships (SARs) are described as well as the rational design strategy employed to overcome the development deficiencies of the first generation ALK inhibitor 4 (TAE684). Compound 15b is currently in phase 1 and phase 2 clinical trials with substantial antitumor activity being observed in ALK-positive cancer patients.

[32]

TÍTULO / TITLE: - Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 1.

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

1200/JCO.2012.44.2806

AUTORES / AUTHORS: - Sequist LV; Yang JC; Yamamoto N; O'Byrne K; Hirsh V; Mok T; Geater SL; Orlov S; Tsai CM; Boyer M; Su WC; Bennouna J; Kato T; Gorbunova V; Lee KH; Shah R; Massey D; Zazulina V; Shahidi M; Schuler M

INSTITUCIÓN / INSTITUTION: - Lecia V. Sequist, Massachusetts General Hospital and Harvard Medical School, Boston, MA; James Chih-Hsin Yang, National Taiwan University Hospital; Chun-Ming Tsai, Taipei Veterans General Hospital, Taipei; Wu-Chou Su, National Cheng Kung University Hospital, Tainan, Taiwan; Nobuyuki Yamamoto, Shizuoka Cancer Center, Shizuoka; Terufumi Kato, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan; Kenneth O'Byrne, St James' Hospital, Dublin, Ireland; Vera Hirsh, McGill University, Montreal, Quebec, Canada; Tony Mok, Prince of Wales Hospital, Hong Kong, China; Sarayut Lucien Geater, Songklanagarind Hospital, Songkla, Thailand; Sergey Orlov, Pavlov State Medical University, St Petersburg; Vera Gorbunova, GU Russian Oncological Research Centre, Moscow, Russia; Michael Boyer, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; Jaafar Bennouna, Institut de Cancerologie de l'Ouest-site Rene Gauducheau, Nantes, France; Ki Hyeong Lee, Chungbuk National University Hospital, Cheongju, South Korea; Riyaz Shah, Maidstone and Tunbridge Wells National Health Service Trust, Maidstone Hospital, Maidstone; Dan Massey, Victoria Zazulina, and Mehdi Shahidi, Boehringer Ingelheim, Bracknell, United Kingdom; and Martin Schuler, West German Cancer Center, University of Duisburg-Essen, Essen, Germany.

RESUMEN / SUMMARY: - **PURPOSE**The LUX-Lung 3 study investigated the efficacy of chemotherapy compared with afatinib, a selective, orally bioavailable ErbB family blocker that irreversibly blocks signaling from epidermal growth factor receptor (EGFR/ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2), and ErbB4 and has wide-spectrum preclinical activity against EGFR mutations. A phase II study of afatinib in EGFR mutation-positive lung adenocarcinoma demonstrated high response rates and progression-free survival (PFS). **PATIENTS AND METHODS**In this phase III study, eligible patients with stage IIIB/IV lung adenocarcinoma were screened for EGFR mutations. Mutation-positive patients were stratified by mutation type (exon 19 deletion, L858R, or other) and race (Asian or non-Asian) before two-to-one random assignment to 40 mg afatinib per day or up to six cycles of cisplatin plus pemetrexed chemotherapy at standard doses every 21 days. The primary end point was PFS by independent review. Secondary end points included tumor response, overall survival, adverse events, and patient-reported outcomes (PROs). **Results**A total of 1,269 patients were screened, and 345 were randomly assigned to treatment. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; P = .001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n = 308) was 13.6 months for afatinib and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; P = .001). The most common treatment-related adverse events were diarrhea, rash/acne, and stomatitis for

afatinib and nausea, fatigue, and decreased appetite for chemotherapy. PROs favored afatinib, with better control of cough, dyspnea, and pain.
CONCLUSION Afatinib is associated with prolongation of PFS when compared with standard doublet chemotherapy in patients with advanced lung adenocarcinoma and EGFR mutations.

[33]

TÍTULO / TITLE: - Long-term remission after multiple relapses in an elderly patient with lymphomatoid granulomatosis after rituximab and high-dose cytarabine chemotherapy without stem-cell transplantation.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 1;31(22):e390-3. doi: 10.1200/JCO.2012.47.4999. Epub 2013 Jun 24.

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

[1200/JCO.2012.47.4999](#)

AUTORES / AUTHORS: - Aoki T; Harada Y; Matsubara E; Morishita T; Suzuki T; Kasai M; Uchida T; Tsuzuki T; Nakamura S; Ogura M

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital 2-9 Myoken-cho, Showa-ku, Nagoya 466-8650, Japan; mi-ogura@naa.att.ne.jp.

[34]

TÍTULO / TITLE: - Clonal chromosomal abnormalities in Philadelphia-negative cells in chronic myeloid leukemia patients treated with nilotinib used in first-line therapy.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jun 23.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1816-](#)

[Z](#)

AUTORES / AUTHORS: - Wang H; Jin J; Wang Y; Huang X; Huang J

INSTITUCIÓN / INSTITUTION: - Department of Hematology, the First Affiliated Hospital, College of Medicine, Zhejiang University, No.79 Qingchun Road, Hangzhou, Zhejiang, 310003, People's Republic of China.

RESUMEN / SUMMARY: - Nilotinib is an effective option for the first-line treatment of chronic myeloid leukemia (CML) patients in chronic phase (CP). In CML patients, clonal cytogenetic abnormalities (CAs) in Philadelphia-negative (Ph-) metaphases have been widely observed after treatment with imatinib, or dasatinib/nilotinib following failure with imatinib. However, such abnormalities in CML patients treated with nilotinib as the first-line therapy have not been reported. Thirteen CML CP patients with Philadelphia-positive (Ph+) cells were initially diagnosed in our hospital from December 2010 to July 2011. Patients were followed up by clinical assessment, cytogenetic analysis, and BCR-ABL

transcriptional level every 3 to 6 months. Retrospective fluorescence in situ hybridization was performed on stored bone marrow specimens of patients when the cytogenetic analysis showed CAs. During nilotinib therapy, 12 (92.3 %), 5 (38.5 %), and 2 (15.4 %) patients achieved complete cytogenetic response, major molecular response, and complete molecular response at 18 months, respectively. Two patients developed CAs in Ph- cells, including trisomy 8 and monosomies 20 and 21. Monosomies 20 and 21 appeared in the same patient simultaneously. Our data confirmed that clonal CAs in Ph- cells is a general phenomenon in Ph+ CML patient treated with tyrosine kinase inhibitors (TKIs), including nilotinib. The clinical significance of these CAs that arise in Ph+ CML patient treated with TKIs and whether these CAs exist before or after treatment of TKIs are not clear.

[35]

TÍTULO / TITLE: - Expression of orphan nuclear receptor NR4A2 in gastric cancer cells confers chemoresistance and predicts an unfavorable postoperative survival of gastric cancer patients with chemotherapy.

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

REVISTA / JOURNAL: - Cancer. 2013 Jul 2. doi: 10.1002/cncr.28228.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28228](#)

AUTORES / AUTHORS: - Han Y; Cai H; Ma L; Ding Y; Tan X; Chang W; Guan W; Liu Y; Shen Q; Yu Y; Zhang H; Cao G

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology, Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - BACKGROUND: NR4A2, an orphan nuclear receptor essential in the generation of dopaminergic neurons, has been recently linked to inflammation and cancer. This study sought to identify the role of NR4A2 on chemoresistance and postoperative prognosis of gastric cancer (GC). METHODS: NR4A2 was transfected into GC cells to investigate its effects on chemoresistance to 5-fluorouracil and the tumorigenicity in nude mice. This study also investigated prostaglandin E2 (PGE2)-induced NR4A2 expression and its effect on chemoresistance. Surgical specimens from patients with stage I through III GC were examined immunohistochemically for NR4A2 expression. Median follow-up time was 76 months for 245 patients. RESULTS: Ectopic expression of NR4A2 significantly increased the chemoresistance and attenuated 5-fluorouracil-induced apoptosis. Transient treatment of GC cells with PGE2 significantly upregulated NR4A2 expression via the protein kinase A pathway and increased the chemoresistance. Ectopic expression of NR4A2 significantly increased the tumorigenicity. In clinical samples, NR4A2 was preferentially expressed in lymphocytes and epithelial cytoplasm in adjacent mucosa. High expression of NR4A2 (immunoreactive score ≥ 3) in cancer cells significantly predicted an unfavorable postoperative disease-specific survival of patients with stage I to III GC ($P = .011$), especially for those who

received 5-fluorouracil-based chemotherapy ($P = .016$). This effect was not found in those without the chemotherapy. In multivariate Cox analyses, age, TNM (tumor/node/metastasis) stage, and high NR4A2 expression significantly predicted an unfavorable postoperative survival. CONCLUSIONS: High NR4A2 expression in GC cells confers chemoresistance, attenuates 5-fluorouracil-induced apoptosis, and predicts an unfavorable survival, especially for those who received chemotherapy. NR4A2 might serve as a prognostic and predictive factor and therapeutic target for patients with GC. Cancer 2013. © 2013 American Cancer Society.

[36]

TÍTULO / TITLE: - Pretreatment CA 15-3 levels do not predict disease-free survival in patients with advanced epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Tumori. 2013 Mar-Apr;99(2):257-60. doi: 10.1700/1283.14201.

●● Enlace al texto completo (gratis o de pago) [1700/1283.14201](#)

AUTORES / AUTHORS: - Gemer O; Oustinov N; Gdalevich M; Dubnik S; Levy R; Yachnin A; Lavie O; Ben Baruch N; Ben Arie A

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, Barzilai Medical Center, Ashkelon, Israel. gemer@barzi.health.gov.il

RESUMEN / SUMMARY: - AIMS: To evaluate the role of pretreatment CA 15-3 levels as a predictor of disease-free survival in patients with advanced epithelial ovarian cancer. METHODS: A cohort of 65 patients with FIGO stage III or IV epithelial ovarian cancer was evaluated. Patients were treated either with primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy or with neoadjuvant chemotherapy with interval debulking surgery. All patients had pretreatment CA 15-3 and CA 125 tumor marker determinations. The patients were divided into a group with elevated CA 15-3 and a group with normal levels. The two groups were compared with regard to clinical and survival measures. RESULTS: The patients' median age was 65 years (range, 37-90); 34 (52%) were at stage III and 31 (48%) at stage IV. CA 15-3 was elevated (>30 units/mL) in 44 (68%) patients, with a median level of 39 units (range, 4-2282). CA 125 was elevated (>35 units/mL) in 61 (94%) patients, with a median level of 947 units (range, 4-30,642). CA 125 and CA 15-3 levels were not correlated ($r = 0.015$, $P = 0.332$). The median follow-up was 22 months (range, 3-120 months). Fifty-three (81%) patients had disease recurrence and 43 (66%) died. Survival analysis showed that patients with elevated and normal CA 15-3 levels had similar recurrence-free survival ($P = 0.78$) and overall survival ($P = 0.55$). CONCLUSIONS: Although elevated in the majority of patients with advanced epithelial ovarian cancer, CA 15-3 levels are not predictive of survival.

[37]

TÍTULO / TITLE: - Detection of leukemia associated antigen-specific cytotoxic T cells in a patient with Philadelphia chromosome-positive leukemia during treatment with dasatinib.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 29.

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

[3109/10428194.2013.812787](#)

AUTORES / AUTHORS: - Matsushita M; Tonegawa K; Mori T; Kohashi S; Kato J; Matsuki E; Okamoto S; Hattori Y

INSTITUCIÓN / INSTITUTION: - Division of Clinical Physiology and Therapeutics, Keio University Faculty of Pharmacy, Tokyo, Japan.

[38]

TÍTULO / TITLE: - Prediction of Late Disease Recurrence and Extended Adjuvant Letrozole Benefit by the HOXB13/IL17BR Biomarker.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Jul 17;105(14):1036-1042. Epub 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt146](#)

AUTORES / AUTHORS: - Sgroi DC; Carney E; Zarrella E; Steffel L; Binns SN; Finkelstein DM; Szymonifka J; Bhan AK; Shepherd LE; Zhang Y; Schnabel CA; Erlander MG; Ingle JN; Porter P; Muss HB; Pritchard KI; Tu D; Rimm DL; Goss PE

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Department of Pathology, Molecular Pathology Unit, Massachusetts General Hospital, Charlestown, MA (DCS, EC, EZ, LOS, SNB, AKB); Department of Pathology and Medicine, Center for Cancer Research, Massachusetts General Hospital, Boston, MA (DCS, EC, EZ, LS, SNB, DMF, JS, PEG); NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada (LES, DT, KIP); bioTheranostics, Inc, San Diego, CA (YZ, CAS, MGE); Mayo Clinic, Rochester, MN (JNI); Human Biology Department, Fred Hutchinson Cancer Research Center, Seattle, WA (PP); Department of Medicine, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC (HBM); Department of Medicine, Sunnybrook Odette Cancer Center, University of Toronto, Toronto, ON, Canada (KIP); Department of Pathology, Yale University School of Medicine, New Haven, CT (DLR).

RESUMEN / SUMMARY: - BACKGROUND: Biomarkers to optimize extended adjuvant endocrine therapy for women with estrogen receptor (ER)-positive breast cancer are limited. The HOXB13/IL17BR (H/I) biomarker predicts recurrence risk in ER-positive, lymph node-negative breast cancer patients. H/I was evaluated in MA.17 trial for prognostic performance for late recurrence and

treatment benefit from extended adjuvant letrozole. METHODS: A prospective-retrospective, nested case-control design of 83 recurrences matched to 166 nonrecurrences from letrozole- and placebo-treated patients within MA.17 was conducted. Expression of H/I within primary tumors was determined by reverse-transcription polymerase chain reaction with a prespecified cutpoint. The predictive ability of H/I for ascertaining benefit from letrozole was determined using multivariable conditional logistic regression including standard clinicopathological factors as covariates. All statistical tests were two-sided. RESULTS: High H/I was statistically significantly associated with a decrease in late recurrence in patients receiving extended letrozole therapy (odds ratio [OR] = 0.35; 95% confidence interval [CI] = 0.16 to 0.75; P = .007). In an adjusted model with standard clinicopathological factors, high H/I remained statistically significantly associated with patient benefit from letrozole (OR = 0.33; 95% CI = 0.15 to 0.73; P = .006). Reduction in the absolute risk of recurrence at 5 years was 16.5% for patients with high H/I (P = .007). The interaction between H/I and letrozole treatment was statistically significant (P = .03). CONCLUSIONS: In the absence of extended letrozole therapy, high H/I identifies a subgroup of ER-positive patients disease-free after 5 years of tamoxifen who are at risk for late recurrence. When extended endocrine therapy with letrozole is prescribed, high H/I predicts benefit from therapy and a decreased probability of late disease recurrence.

[39]

TÍTULO / TITLE: - A prognostic model based on combining estrogen receptor expression and Ki-67 value after neoadjuvant chemotherapy predicts clinical outcome in locally advanced breast cancer: Extension and analysis of a previously reported cohort of patients.

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

REVISTA / JOURNAL: - Eur J Surg Oncol. 2013 Jul 25. pii: S0748-7983(13)00544-1. doi: 10.1016/j.ejso.2013.06.024.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.06.024](#)

AUTORES / AUTHORS: - Miglietta L; Morabito F; Provinciali N; Canobbio L; Meszaros P; Naso C; Murialdo R; Boitano M; Salvi S; Ferrarini M

INSTITUCIÓN / INSTITUTION: - S.C. Oncologia Medica A, IRCCS AOU San Martino - IST, Genoa, Italy. Electronic address: loredana.miglietta@hsanmartino.it.

RESUMEN / SUMMARY: - BACKGROUND: Ki-67 expression has gained attention as a breast cancer prognostic factor, however its significance in the remaining malignant cells after neoadjuvant chemotherapy (NAC) has been rarely examined. This investigation, extension and analysis of a previously reported cohort of patients, evaluates the significance of Ki-67 and estrogen receptor (ER) expression after NAC in LABC (locally advanced breast cancer).

PATIENTS AND METHODS: clinical stage, tumor size, clinical and pathological

lymph node involvement, Ki-67, ER, progesterone receptor (PgR), HER2 expression, grading and clinical response were evaluated before and after NAC in 110 patients with LABC. Ki-67 expression was assessed both in pre and post-therapy histological samples, using >15% positive cells as cut-off value to distinguish high from low Ki-67 expressing tumors. RESULTS: six patients (5.45%) attained pCR after NAC. A significant relationship between elevated post-CT Ki-67 and ER expression was showed at Cox multivariate analysis of disease free survival (DFS). On univariate analysis high post-chemotherapy Ki-67 and ER status were associated with worse survival; at multivariate model included these results were confirmed. Based on these two parameters, a prognostic model identified two different groups: low risk (low postchemotherapy Ki-67 and ER positive, or either high post-chemotherapy Ki-67 or ER negative), and high risk (high post-chemotherapy Ki-67 and ER negative). The low risk group showed a good prognosis (median OS still not reached), while the high risk group had a worse OS (median 41 months). CONCLUSIONS: Ki-67 value after NAC and ER status could predict a worse prognosis among LABC patients treated with NAC.

[40]

TÍTULO / TITLE: - The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - Analysis of patient data in the prospective OVCAD study.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Jul 20. pii: S0090-8258(13)01006-8. doi: 10.1016/j.ygyno.2013.07.086.

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

1016/j.ygyno.2013.07.086

AUTORES / AUTHORS: - Hofstetter G; Concin N; Braicu I; Chekerov R; Sehouli J; Cadron I; Van Gorp T; Trillsch F; Mahner S; Ulmer H; Grimm C; Castillo-Tong DC; Zeillinger R; Zeimet AG; Vergote I

INSTITUCIÓN / INSTITUTION: - Department of Gynecology and Obstetrics, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria.

RESUMEN / SUMMARY: - OBJECTIVE: Cytoreductive surgery and platinum-based systemic therapy constitute the standard treatment of patients with advanced ovarian cancer. The aim of the present study was to evaluate whether the time interval from surgery to start of chemotherapy has an impact on clinical outcome. METHODS: Data of 191 patients with advanced serous (FIGO III-IV) ovarian cancer from the prospective multicenter study OVCAD (OVarian CAncer Diagnosis) were analyzed. All patients underwent primary surgery followed by platinum-based chemotherapy. RESULTS: The 25%, 50%, and 75% quartiles of intervals from surgery to start of chemotherapy were 22, 28, and 38days, respectively (range, 4-158days). Preoperative performance status ($P<0.001$), extent of surgery ($P<0.001$), and perioperative complications

($P < 0.001$) correlated with intervals from surgery to initiation of chemotherapy. Timing of cytotoxic treatment [≤ 28 days versus > 28 days; hazard ratio (HR) 1.73 (95% confidence interval 1.08-2.78), $P = 0.022$], residual disease [HR 2.95 (95% confidence interval 1.87-4.67), $P < 0.001$], and FIGO stage [HR 2.26 (95% confidence interval 1.41-3.64), $P = 0.001$] were significant prognostic factors for overall survival in multivariate analysis. While the interval from surgery to start of chemotherapy did not possess prognostic significance in patients without postoperative residual disease ($n = 121$), it significantly correlated with overall survival in patients with postoperative residual disease [$n = 70$, HR 2.24 (95% confidence interval 1.08-4.66), $P = 0.031$]. CONCLUSION: Our findings suggest that delayed initiation of chemotherapy might compromise overall survival in patients with advanced serous ovarian cancer, especially when suboptimally debulked.

[41]

TÍTULO / TITLE: - The role of aberrant VHL/HIF pathway elements in predicting clinical outcome to pazopanib therapy in patients with metastatic clear-cell renal cell carcinoma.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 23.

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0491](#)

AUTORES / AUTHORS: - Choueiri TK; Fay A; Gagnon R; Lin Y; Bahamon B; Brown VE; Rosenberg J; Hutson TE; Baker-Neblett K; Carpenter C; Liu Y; Pandite L; Signoretti S

INSTITUCIÓN / INSTITUTION: - Medical Oncology, Dana-Farber Cancer Institute.

RESUMEN / SUMMARY: - PURPOSE: Inactivation of von Hippel-Lindau (VHL) gene in clear-cell renal cell carcinoma (RCC) leads to increased levels of hypoxia-inducible factors (HIFs) and overexpression of HIF target genes, such as vascular endothelial growth factor (VEGF) and others. VEGF-targeted agents are standard in advanced clear-cell RCC but biomarkers of activity are lacking. EXPERIMENTAL DESIGN: We analyzed tumor tissue samples from metastatic clear-cell RCC patients who received pazopanib as part of clinical trial VEG102616. We evaluated several components of the VHL/HIF pathway: VHL gene inactivation (mutation and/or methylation), HIF1alpha and HIF2alpha immunohistochemistry staining, and HIF1alpha transcriptional signature. We evaluated the association of these biomarkers with best overall response rate and progression-free survival to pazopanib, a standard first-line VEGF-targeted agent. RESULTS: The VEG102616 trial enrolled 225 patients, from whom 78 samples were available for tumor DNA extraction. Of these, 70 patients had VHL mutation or methylation. VHL gene status did not correlate with overall response rate or progression-free survival. Similarly, HIF1alpha (65 samples) and HIF2alpha (66 samples) protein levels (high vs. low) did not correlate with

overall response rate or progression-free survival to pazopanib. The HIF1alpha transcriptional signature (46 samples) was enriched in tumors expressing high HIF1alpha levels. However, the HIF1alpha gene expression signature was not associated with clinical outcome to pazopanib. CONCLUSIONS: In patients with advanced clear-cell RCC, several potential biomarkers along the VHL/HIF1alpha/HIF2alpha axis were not found to be predictive for pazopanib activity. Additional efforts must continue to identify biomarkers associated with clinical outcome to VEGF-targeted agents in metastatic RCC.

[42]

TÍTULO / TITLE: - The outcome of patients with low risk gestational trophoblastic neoplasia treated with single agent intramuscular methotrexate and oral folinic acid.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jul 16. pii: S0959-8049(13)00464-4. doi: 10.1016/j.ejca.2013.06.004.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.ejca.2013.06.004](#)

AUTORES / AUTHORS: - Taylor F; Grew T; Everard J; Ellis L; Winter MC; Tidy J; Hancock BW; Coleman RE

INSTITUCIÓN / INSTITUTION: - Sheffield Centre for Trophoblastic Disease, Weston Park Hospital, Cancer Research-UK/Yorkshire Cancer Research Sheffield Cancer Research Centre, Sheffield, UK. Electronic address: F.Taylor@sheffield.ac.uk.

RESUMEN / SUMMARY: - BACKGROUND: Gestational trophoblastic neoplasia (GTN) persisting despite local treatment requires chemotherapy. In 2000, the revised International Federation of Gynaecology and Obstetrics (FIGO)/World Health Organisation (WHO) staging system was introduced, classifying patients as at 'low' or 'high' risk for resistance to single agent treatment. PATIENTS AND METHODS: We have evaluated the complete response rates of patients with low risk GTN treated with 2 weekly intramuscular (IM) methotrexate 50mg four doses days 1, 3, 5, 7 and oral folinic acid 15mg days 2, 4, 6, 8 (MTX/FA). Patient data between January 2000 and December 2011 were collated and the relationships between FIGO/WHO risk score and outcomes evaluated. RESULTS: Two hundred and eighty nine patients were treated with single agent IM MTX/FA and assessed for treatment response. 29/36 (81%) patients with a FIGO/WHO total score of 6 developed resistance to MTX/FA compared with 87/253 (34%) patients with a score of 0-5 (p0.0001). Significantly higher rates of resistance were found for patients with an hCG level of >100,000iu/l compared to an hCG level of <100,000iu/l (84% versus 34% p0.0001). All patients were eventually cured with chemotherapy or surgical salvage. CONCLUSIONS: Patients with low risk GTN that have a FIGO/WHO score of 6 or hCG level of >100,000iu/l have high rates of resistance to MTX/FA and require further

treatment. Revision of the FIGO/WHO scoring system may be appropriate to enable selection of more effective first line chemotherapy.

[43]

TÍTULO / TITLE: - Somatic profiling of the epidermal growth factor receptor pathway in tumors from patients with advanced colorectal cancer treated with chemotherapy {+/-} cetuximab.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4104-13. doi: 10.1158/1078-0432.CCR-12-2581. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-2581](#)

AUTORES / AUTHORS: - Smith CG; Fisher D; Claes B; Maughan TS; Idziaszczyk S; Peuteman G; Harris R; James MD; Meade A; Jasani B; Adams RA; Kenny S; Kaplan R; Lambrechts D; Cheadle JP

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, Wales; MRC Clinical Trials Unit, London; Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford, United Kingdom; Vesalius Research Center, VIB; and Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium.

RESUMEN / SUMMARY: - **PURPOSE:** To study the somatic molecular profile of the EGF receptor (EGFR) pathway in advanced colorectal cancer, its relationship to prognosis, the site of the primary and metastases, and response to cetuximab. **EXPERIMENTAL DESIGN:** We used Sequenom and Pyrosequencing for high-throughput somatic profiling of the EGFR pathway in 1,976 tumors from patients with advanced colorectal cancer from the COIN trial (oxaliplatin and fluoropyrimidine chemotherapy +/- cetuximab). Correlations between mutations, clinicopathologic, response, and survival data were carried out. **RESULTS:** Sequenom and Pyrosequencing had 99.0% (9,961/10,063) genotype concordance. We identified 13 different KRAS mutations in 42.3% of advanced colorectal cancers, 2 BRAF mutations in 9.0%, 4 NRAS mutations in 3.6%, and 5 PIK3CA mutations in 12.7%. 4.2% of advanced colorectal cancers had microsatellite instability (MSI). KRAS and PIK3CA exon 9, but not exon 20, mutations cooccurred ($P = 8.9 \times 10^{-4}$) as did MSI and BRAF mutations ($P = 5.3 \times 10^{-10}$). KRAS mutations were associated with right colon cancers ($P = 5.2 \times 10^{-5}$) and BRAF mutations with right ($P = 7.2 \times 10^{-5}$) and transverse colon ($P = 9.8 \times 10^{-6}$) cancers. KRAS mutations were associated with lung-only metastases ($P = 2.3 \times 10^{-4}$), BRAF mutations with peritoneal ($P = 9.2 \times 10^{-4}$) and nodal-only ($P = 3.7 \times 10^{-5}$) metastases, and MSI (BRAF(WT)) with nodal-only metastases ($P = 2.9 \times 10^{-4}$). MSI (BRAF(WT)) was associated with worse survival (HR = 1.89, 95% CI 1.30-2.76, $P = 8.5 \times 10^{-4}$). No mutations, subsets of mutations, or MSI status were associated with response to

cetuximab. CONCLUSIONS: Our data support a functional cooperation between KRAS and PIK3CA in colorectal tumorigenesis and link somatic profiles to the sites of metastases. MSI was associated with poor prognosis in advanced disease, and no individual somatic profile was associated with response to cetuximab in COIN. Clin Cancer Res; 19(15); 4104-13. ©2013 AACR.

[44]

TÍTULO / TITLE: - Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myelome experience.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 1;31(22):2806-9. doi: 10.1200/JCO.2012.46.2598. Epub 2013 Jun 24.

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

[1200/JCO.2012.46.2598](#)

AUTORES / AUTHORS: - Avet-Loiseau H; Hulin C; Campion L; Rodon P; Marit G; Attal M; Royer B; Dib M; Voillat L; Bouscary D; Caillot D; Wetterwald M; Pegourie B; Lepeu G; Corront B; Karlin L; Stoppa AM; Fuzibet JG; Delbrel X; Guilhot F; Kolb B; Decaux O; Lamy T; Garderet L; Allangba O; Lifermann F; Anglaret B; Moreau P; Harousseau JL; Facon T

INSTITUCIÓN / INSTITUTION: - Unite de Genomique du Myelome, CHU Ranguel, 31059 Toulouse, France; avet-loiseau.h@chu-toulouse.fr.

RESUMEN / SUMMARY: - PURPOSE Chromosomal abnormalities, especially t(4;14) and del(17p), are major prognostic factors in patients with multiple myeloma (MM). However, this has been especially demonstrated in patients age < 66 years treated with intensive approaches. The goal of this study was to address this issue in elderly patients treated with conventional-dose chemotherapy. PATIENTS AND METHODS To answer this important question, we retrospectively analyzed a series of 1,890 patients (median age, 72 years; range, 66 to 94 years), including 1,095 with updated data on treatment modalities and survival. Results This large study first showed that the incidence of t(4;14) was not uniform over age, with a marked decrease in the oldest patients. Second, it showed that both t(4;14) and del(17p) retained their prognostic value in elderly patients treated with melphalan and prednisone-based chemotherapy. CONCLUSION t(4;14) and del(17p) are major prognostic factors in elderly patients with MM, both for progression-free and overall survival, indicating that these two abnormalities should be investigated at diagnosis of MM, regardless of age.

[45]

TÍTULO / TITLE: - The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial.

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

REVISTA / JOURNAL: - Lancet Oncol. 2013 Aug;14(9):882-92. doi: 10.1016/S1470-2045(13)70240-7. Epub 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1016/S1470-2045\(13\)70240-7](#)

AUTORES / AUTHORS: - Sandhu SK; Schelman WR; Wilding G; Moreno V; Baird RD; Miranda S; Hylands L; Riisnaes R; Forster M; Omlin A; Kreischer N; Thway K; Gevensleben H; Sun L; Loughney J; Chatterjee M; Toniatti C; Carpenter CL; Iannone R; Kaye SB; de Bono JS; Wenham RM

INSTITUCIÓN / INSTITUTION: - The Institute of Cancer Research, Sutton, Surrey, UK; Drug Development Unit, Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.

RESUMEN / SUMMARY: - BACKGROUND: Poly(ADP-ribose) polymerase (PARP) is implicated in DNA repair and transcription regulation. Niraparib (MK4827) is an oral potent, selective PARP-1 and PARP-2 inhibitor that induces synthetic lethality in preclinical tumour models with loss of BRCA and PTEN function. We investigated the safety, tolerability, maximum tolerated dose, pharmacokinetic and pharmacodynamic profiles, and preliminary antitumour activity of niraparib. METHODS: In a phase 1 dose-escalation study, we enrolled patients with advanced solid tumours at one site in the UK and two sites in the USA. Eligible patients were aged at least 18 years; had a life expectancy of at least 12 weeks; had an Eastern Cooperative Oncology Group performance status of 2 or less; had assessable disease; were not suitable to receive any established treatments; had adequate organ function; and had discontinued any previous anticancer treatments at least 4 weeks previously. In part A, cohorts of three to six patients, enriched for BRCA1 and BRCA2 mutation carriers, received niraparib daily at ten escalating doses from 30 mg to 400 mg in a 21-day cycle to establish the maximum tolerated dose. Dose expansion at the maximum tolerated dose was pursued in 15 patients to confirm tolerability. In part B, we further investigated the maximum tolerated dose in patients with sporadic platinum-resistant high-grade serous ovarian cancer and sporadic prostate cancer. We obtained blood, circulating tumour cells, and optional paired tumour biopsies for pharmacokinetic and pharmacodynamic assessments. Toxic effects were assessed by common toxicity criteria and tumour responses ascribed by Response Evaluation Criteria in Solid Tumors (RECIST). Circulating tumour cells and archival tumour tissue in prostate patients were analysed for exploratory putative predictive biomarkers, such as loss of PTEN expression and ETS rearrangements. This trial is registered with ClinicalTrials.gov, NCT00749502. FINDINGS: Between Sept 15, 2008, and Jan 14, 2011, we enrolled 100 patients: 60 in part A and 40 in part B. 300 mg/day was established as the maximum tolerated dose. Dose-limiting toxic effects reported

in the first cycle were grade 3 fatigue (one patient given 30 mg/day), grade 3 pneumonitis (one given 60 mg/day), and grade 4 thrombocytopenia (two given 400 mg/day). Common treatment-related toxic effects were anaemia (48 patients [48%]), nausea (42 [42%]), fatigue (42 [42%]), thrombocytopenia (35 [35%]), anorexia (26 [26%]), neutropenia (24 [24%]), constipation (23 [23%]), and vomiting (20 [20%]), and were predominantly grade 1 or 2. Pharmacokinetics were dose proportional and the mean terminal elimination half-life was 36.4 h (range 32.8-46.0). Pharmacodynamic analyses confirmed PARP inhibition exceeded 50% at doses greater than 80 mg/day and antitumour activity was documented beyond doses of 60 mg/day. Eight (40% [95% CI 19-64]) of 20 BRCA1 or BRCA2 mutation carriers with ovarian cancer had RECIST partial responses, as did two (50% [7-93]) of four mutation carriers with breast cancer. Antitumour activity was also reported in sporadic high-grade serous ovarian cancer, non-small-cell lung cancer, and prostate cancer. We recorded no correlation between loss of PTEN expression or ETS rearrangements and measures of antitumour activity in patients with prostate cancer. INTERPRETATION: A recommended phase 2 dose of 300 mg/day niraparib is well tolerated. Niraparib should be further assessed in inherited and sporadic cancers with homologous recombination DNA repair defects and to target PARP-mediated transcription in cancer. FUNDING: Merck Sharp and Dohme.

[46]

TÍTULO / TITLE: - Epidermal growth factor receptor expression in laryngeal cancer predicts the effect of hypoxia modification as an additive to accelerated radiotherapy in a randomised controlled trial.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jul 15. pii: S0959-8049(13)00499-1. doi: 10.1016/j.ejca.2013.06.024.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.06.024](#)

AUTORES / AUTHORS: - Nijkamp MM; Span PN; Terhaard CH; Doornaert PA; Langendijk JA; van den Ende PL; de Jong M; van der Kogel AJ; Bussink J; Kaanders JH

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

RESUMEN / SUMMARY: - Accelerated radiotherapy (AR) improves the poor prognosis associated with epidermal growth factor receptor (EGFR) overexpression frequently seen in head and neck carcinomas. Combining AR with carbogen and nicotinamide (ARCON) counteracts enhanced tumour cell proliferation- and hypoxia-related radioresistance. The purpose of this study was to investigate if EGFR expression levels are associated with response to ARCON in patients with carcinoma of the larynx. Patients (N=272) with advanced stage larynx carcinoma were randomised between AR alone and

ARCON. Paraffin-embedded biopsies from these patients were processed for immunohistochemical staining of EGFR. EGFR fraction was quantitated by automated image analysis and related to clinical outcome. A large variation was observed in EGFR fraction between tumours with expression levels ranging from 0 to 0.93 (median fraction 0.4). No difference in 5-year locoregional control was found between low and high EGFR expressing tumours in the AR arm (69% versus 75%), which is in line with the established effect of AR in EGFR overexpressing tumours. There was, however, a significant association in the ARCON arm: patients with low EGFR levels had a better 5-year locoregional control (88% versus 72% p=0.02) and disease-specific survival (92% versus 77% p=0.01). ARCON improved locoregional control relative to AR only in patients with low EGFR expression (hazard ratio (HR) 0.34 p=0.009). In conclusion, only in tumours with a low EGFR fraction, adding hypoxia modification to AR has an additive beneficial effect on outcome. EGFR expression is a predictive biomarker for the selection of patients that will or will not respond to ARCON.

[47]

TÍTULO / TITLE: - Epithelial Membrane Protein 2 Is a Prognostic Indicator for Patients with Urothelial Carcinoma of the Upper Urinary Tract.

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

REVISTA / JOURNAL: - Am J Pathol. 2013 Jul 6. pii: S0002-9440(13)00401-X. doi: 10.1016/j.ajpath.2013.05.015.

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

[1016/j.ajpath.2013.05.015](#)

AUTORES / AUTHORS: - Wang YW; Li WM; Wu WJ; Chai CY; Chang TY; Sun Y; Cheng CJ; Shiue YL; Su SJ; Cheng HL; Liu HS; Chow NH

INSTITUCIÓN / INSTITUTION: - Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

RESUMEN / SUMMARY: - Upper urinary tract urothelial carcinoma is a relatively uncommon disease and is diagnosed more frequently at advanced stages. The prognosis of these patients mainly has been related to tumor stage and grade. As a result, the definition of prognostic indicators enabling precise patient selection is mandatory for neoadjuvant or adjuvant therapies. The epithelial membrane protein (EMP2) was identified as one of the up-regulated genes by isoflavones. EMP2 overexpression suppressed foci formation, anchorage-independent growth in vitro, and tumorigenicity in severe combined immunodeficiency mice (all P < 0.05). In addition, a cross-talk between EMP2 and integrins alphaV and beta3 was shown in the regulation of cell adhesion and migration. Higher EMP2 expression was associated with a better progression-free survival (P = 0.008) and cancer-related death (P < 0.001). EMP2 was identified as a tumor-suppressor gene in urinary tract urothelial

carcinoma and may be an innovative co-targeting candidate for designing integrin-based cancer therapy.

[48]

TÍTULO / TITLE: - Dosimetric parameters predictive of acute gastrointestinal toxicity in patients with anal carcinoma treated with concurrent chemotherapy and intensity-modulated radiation therapy.

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

REVISTA / JOURNAL: - Oncology. 2013;85(1):1-7. doi: 10.1159/000348387. Epub 2013 Jun 1.

●● Enlace al texto completo (gratis o de pago) [1159/000348387](#)

AUTORES / AUTHORS: - Defoe SG; Kabolizadeh P; Heron DE; Beriwal S

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, Pa., USA.

RESUMEN / SUMMARY: - Objective: To determine the dosimetric parameters predictive of acute gastrointestinal (GI) toxicity in anal cancer patients treated with intensity-modulated radiotherapy (IMRT) and concurrent chemotherapy. Methods: Fifty-eight anal cancer patients were treated with concurrent chemotherapy and IMRT. The bowel was delineated on the planning CT and included the intestinal cavity. Regression models with multiple independent predictors were used to test associations of clinical factors and dosimetric parameters with clinically significant GI toxicity (grade ≥ 3). Significant dosimetric factors were fitted to a normal tissue complication probability curve using a logit function and subsequently analyzed at multiple bowel volumes to determine the threshold for clinically significant GI toxicity. Results: Two patients (3.4%) experienced no acute GI toxicity, whereas 20 (34.5%) experienced grade 1 toxicity, 20 (34.5%) experienced grade 2, 16 (27.6%) experienced grade 3 and none experienced grade 4. Analysis showed that the volumes of bowel receiving 30 Gy (V30) and 40 Gy (V40) both correlated with clinically significant acute GI toxicity. In patients whose V30 was $>310 \text{ cm}^3$, the rate of clinically significant acute GI toxicity was 38.9%, compared to 9.1% if V30 was $\leq 310 \text{ cm}^3$ ($p = 0.016$). If V40 was $\leq 70 \text{ cm}^3$, the rate of acute grade ≥ 3 toxicity was 6.3%, versus 35.7% if V40 was $>70 \text{ cm}^3$ ($p = 0.045$). Conclusion: This analysis demonstrates that the bowel dosimetric parameters are associated with clinically significant acute GI toxicity when IMRT is used in the management of anal cancer patients.

[49]

TÍTULO / TITLE: - Multicenter validation study of pathologic response and tumor thickness at the tumor-normal liver interface as independent predictors of disease-free survival after preoperative chemotherapy and surgery for colorectal liver metastases.

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

REVISTA / JOURNAL: - Cancer. 2013 Aug 1;119(15):2778-88. doi: 10.1002/cncr.28097. Epub 2013 Apr 23.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28097](#)

AUTORES / AUTHORS: - Brouquet A; Zimmitti G; Kopetz S; Stiff J; Julie C; Lemaistre AI; Agarwal A; Patel V; Benoist S; Nordlinger B; Gandini A; Rivoire M; Stremitzer S; Gruenberger T; Vauthey JN; Maru DM

INSTITUCIÓN / INSTITUTION: - Department of Digestive Surgery and Surgical Oncology, Ambroise Pare Hospital, Boulogne-Billancourt, France.

RESUMEN / SUMMARY: - BACKGROUND: To validate pathologic markers of response to preoperative chemotherapy as predictors of disease-free survival (DFS) after resection of colorectal liver metastases (CLM). METHODS: One hundred seventy-one patients who underwent resection of CLM after preoperative chemotherapy at 4 centers were studied. Pathologic response-defined as the proportion of tumor cells remaining (complete, 0%; major, <50%; minor, \geq 50%) and tumor thickness at the tumor-normal liver interface (TNI) (<0.5 mm, 0.5 to <5 mm, \geq 5 mm)-was assessed by a central pathology reviewer and local pathologists. RESULTS: Pathologic response was complete in 8% of patients, major in 49% of patients, and minor in 43% of patients. Tumor thickness at the TNI was <0.5 mm in 21% of patients, 0.5 to <5 mm in 56% of patients, and \geq 5 mm in 23% of patients. On multivariate analyses, using either pathologic response or tumor thickness at TNI, pathologic response (P = .002, .009), tumor thickness at TNI (P = 0.015, <.001), duration of preoperative chemotherapy (P = .028, .043), number of CLM (P = .038, .037), and margin (P = .011, .016) were associated with DFS. In a multivariate analysis using both parameters, tumor thickness at TNI (P = .004, .015), duration of preoperative chemotherapy (P = .025), number of nodules (P = .027), and margin (P = .014) were associated with DFS. Tumor size by pathology examination was the predictor of pathologic response. Predictors of tumor thickness at the TNI were tumor size and chemotherapy regimen. There was near perfect agreement for pathologic response (kappa = .82) and substantial agreement (kappa = .76) for tumor thickness between the central reviewer and local pathologists. CONCLUSIONS: Pathologic response and tumor thickness at the TNI are valid predictors of DFS after preoperative chemotherapy and surgery for CLM. Cancer 2013;119:2778-2788. © 2013 American Cancer Society.

[50]

TÍTULO / TITLE: - A multinational phase II trial of bevacizumab with low-dose interferon-alpha2a as first-line treatment of metastatic renal cell carcinoma: BEVLIN.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt228](#)

AUTORES / AUTHORS: - Melichar B; Bracarda S; Matveev V; Alekseev B; Ivanov S; Zyryanov A; Janciauskiene R; Fernebro E; Mulders P; Osborne S; Jethwa S; Mickisch G; Gore M; van Moorselaar RJ; Staehler M; Magne N; Bellmunt J

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic.

RESUMEN / SUMMARY: - BACKGROUND: Avastin and Roferon in Renal Cell Carcinoma (AVOREN) demonstrated efficacy for bevacizumab plus interferon-alpha2a (IFN; 9 MIU tiw) in first-line metastatic renal cell carcinoma (mRCC). We evaluated bevacizumab with low-dose IFN in mRCC to determine whether clinical benefit could be maintained with reduced toxicity. METHODS: BEVLIN was an open-label, single-arm, multinational, phase II trial. Nephrectomized patients with treatment-naive, clear cell mRCC and favourable/intermediate Memorial Sloan-Kettering Cancer Center scores received bevacizumab (10 mg/kg every 2 weeks) and IFN (3 MIU thrice weekly) until disease progression. Descriptive comparisons with AVOREN patients having favourable/intermediate MSKCC scores treated with bevacizumab plus IFN (9 MIU) were made. Primary end points were grade ≥ 3 IFN-associated adverse events (AEs) and progression-free survival (PFS). All grade ≥ 3 AEs and bevacizumab/IFN-related grade 1-2 AEs occurring from first administration until 28 days after last treatment were reported. RESULTS: A total of 146 patients were treated; the median follow-up was 29.4 months. Any-grade and grade ≥ 3 IFN-associated AEs occurred in 53.4% and 10.3% of patients, respectively. The median PFS and overall survival were 15.3 [95% confidence interval (CI): 11.7-18.0] and 30.7 months (95% CI: 25.7-not reached), respectively. The ORR was 28.8%. CONCLUSIONS: Compared with a historical control AVOREN subgroup, low-dose IFN with bevacizumab resulted in a reduction in incidence rates of IFN-related AEs, without compromising efficacy [NCT00796757].

[51]

TÍTULO / TITLE: - CYP2C19*2 predicts substantial tamoxifen benefit in postmenopausal breast cancer patients randomized between adjuvant tamoxifen and no systemic treatment.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jun;139(3):649-55. doi: 10.1007/s10549-013-2568-0. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2568-](#)

[0](#)

AUTORES / AUTHORS: - Beelen K; Opdam M; Severson TM; Koornstra RH; Vincent AD; Hauptmann M; van Schaik RH; Berns EM; Vermorken JB; van Diest PJ; Linn SC

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology and Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands, k.beelen@nki.nl.

RESUMEN / SUMMARY: - Estrogen catabolism is a major function of CYP2C19. The effect of CYP2C19 polymorphisms on tamoxifen sensitivity may therefore not only be mediated by a variation in tamoxifen metabolite levels but also by an effect on breast cancer risk and molecular subtype due to variation in lifelong exposure to estrogens. We determined the association between these polymorphisms and tamoxifen sensitivity in the context of a randomized trial, which allows for the discernment of prognosis from prediction. We isolated primary tumor DNA from 535 estrogen receptor-positive, stages I-III, postmenopausal breast cancer patients who had been randomized to tamoxifen (1-3 years) or no adjuvant therapy. Recurrence-free interval improvement with tamoxifen versus control was assessed according to the presence or absence of CYP2C19*2 and CYP2C19*17. Hazard ratios and interaction terms were calculated using multivariate Cox proportional hazard models, stratified for nodal status. Tamoxifen benefit was not significantly affected by CYP2C19*17. Patients with at least one CYP2C19*2 allele derived significantly more benefit from tamoxifen (HR 0.26; p = 0.001) than patients without a CYP2C19*2 allele (HR 0.68; p = 0.18) (p for interaction 0.04). In control patients, CYP2C19*2 was an adverse prognostic factor. In conclusion, breast cancer patients carrying at least one CYP2C19*2 allele have an adverse prognosis in the absence of adjuvant systemic treatment, which can be substantially improved by adjuvant tamoxifen treatment.

[52]

TÍTULO / TITLE: - Putative Predictive Biomarkers of Survival in Patients with Metastatic Pancreatic Adenocarcinoma Treated with Gemcitabine and Ganitumab, an IGF1R Inhibitor.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4282-9. doi: 10.1158/1078-0432.CCR-12-1840. Epub 2013 Jun 5.

- [Enlace al texto completo \(gratis o de pago\) 1158/1078-0432.CCR-12-1840](#)

AUTORES / AUTHORS: - McCaffery I; Tudor Y; Deng H; Tang R; Suzuki S; Badola S; Kindler HL; Fuchs CS; Loh E; Patterson SD; Chen L; Gansert JL

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Amgen Inc., Thousand Oaks; Amgen Inc., South San Francisco, California; Amgen Inc., Cambridge; Dana-Farber Cancer Institute, Boston, Massachusetts; and University of Chicago Medical Center, Chicago, Illinois.

RESUMEN / SUMMARY: - **PURPOSE:** This planned exploratory analysis assessed the predictive nature of baseline circulating factors of the insulin-like growth factor (IGF) axis on the treatment effect of ganitumab (monoclonal antibody inhibitor of IGF-1 receptor) plus gemcitabine in a randomized phase II study in metastatic pancreatic adenocarcinoma. **EXPERIMENTAL DESIGN:** Baseline levels of IGFs/IGF binding proteins (IGFBP) were analyzed in serum or plasma.

Mutations and gene expression were analyzed in archival samples. Treatment effects between biomarker subgroups were compared for overall survival (OS). Associations of tumor markers with OS were evaluated. RESULTS: For patients with evaluable samples, ganitumab was associated with improved OS versus placebo (HR, 0.49; 95% CI: 0.28-0.87). The treatment effect on improved OS was strong in the patient subset with higher levels of IGF-1, IGF-2, or IGFBP-3, or lower levels of IGFBP-2, but not so on the other corresponding subset. Median OS of ganitumab versus placebo in patients with higher levels of IGF-1, IGF-2, and IGFBP-3 was 16 versus 6.8 months (HR, 0.25; 95% CI: 0.09-0.67), 16 versus 5.9 months (HR, 0.24; 95% CI: 0.09-0.68), and 16 versus 6.8 months (HR, 0.28; 95% CI: 0.11-0.73), and in patients with lower IGFBP-2 levels was 12.7 versus 6.6 months (HR, 0.19; 95% CI: 0.07-0.55). Interaction between treatment and IGFs/IGFBPs in multivariate analyses suggested predictive potential for IGF-2 (P = 0.002) and IGFBP-2 (P = 0.02). KRAS mutation status and PTEN expression were not associated with OS. CONCLUSIONS: Baseline circulating factors of the IGF axis may predict OS benefit from ganitumab plus gemcitabine in metastatic pancreatic adenocarcinoma. Clin Cancer Res; 19(15); 4282-9. ©2013 AACR.

[53]

TÍTULO / TITLE: - VEGF-A polymorphisms predict progression-free survival among advanced castration-resistant prostate cancer patients treated with metronomic cyclophosphamide.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 16. doi: 10.1038/bjc.2013.398.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.398](#)

AUTORES / AUTHORS: - Orlandi P; Fontana A; Fioravanti A; Di Desidero T; Galli L; Derosa L; Canu B; Marconcini R; Biasco E; Solini A; Francia G; Danesi R; Falcone A; Bocci G

INSTITUCIÓN / INSTITUTION: - 1] Division of Pharmacology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy [2] Istituto Toscano Tumori (ITT), Florence, Italy.

RESUMEN / SUMMARY: - Background: No data are available on the pharmacogenetics of metronomic chemotherapy in prostate cancer. The aim of this study was to evaluate the association between VEGF-A sequence variants and prostate-specific antigen (PSA) progression, progression-free survival (PFS) and overall survival (OS), in advanced castration-resistant prostate cancer patients treated with metronomic cyclophosphamide (CTX), celecoxib and dexamethasone. Methods: Forty-three patients were enrolled, and genomic DNA was extracted. VEGF-A gene SNPs (-2578^a/C, -634C/G, +936C/T) were analysed using TaqMan PCR assays. Hardy-Weinberg equilibrium was tested for each SNP, and genetic effects were evaluated by Fisher's exact test. PFS and OS were analysed with GraphPad Prism software, using the product limit

method of Kaplan and Meier, and comparing survival curves using both the log-rank test and the Gehan-Wilcoxon test. We used Bonferroni correction to account for multiple testing, and a two-tailed P-value of <0.017 was considered statistically significant. Results: Overall, 20 patients (46%) experienced a reduction in PSA levels from baseline and, among them, 14 (32%) showed a confirmed PSA \geq 50% decrease. In non-responders, the -2578CC genotype was more frequent (18.60% vs 2.33% in responders; P=0.0212) whereas the -634CC genotype frequency was 22.73% vs 0% in responders (P=0.0485). With regard to PFS, patients harbouring the -634CC genotype had a median PFS of 2.2 months whereas patients with the genotype -634CG/GG had a median PFS of 6.25 months (P=0.0042). Conclusion: The -634CC genotype is significantly associated with a shorter PFS in patients treated with a metronomic CTX schedule. British Journal of Cancer advance online publication 16 July 2013; doi:10.1038/bjc.2013.398 www.bjcancer.com.

[54]

TÍTULO / TITLE: - Epidermal growth factor receptor tyrosine kinase inhibitors as initial therapy for non-small cell lung cancer: Focus on epidermal growth factor receptor mutation testing and mutation-positive patients.

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

REVISTA / JOURNAL: - Cancer Treat Rev. 2013 Jun 12. pii: S0305-7372(13)00093-5. doi: 10.1016/j.ctrv.2013.05.001.

●● Enlace al texto completo (gratis o de pago) 1016/j.ctrv.2013.05.001

AUTORES / AUTHORS: - Roengvoraphoj M; Tsongalis GJ; Dragnev KH; Rigas JR

INSTITUCIÓN / INSTITUTION: - Comprehensive Thoracic Oncology Program, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756-0001, USA; The Geisel School of Medicine at Dartmouth, One Rope Ferry Road, Hanover, NH 03755-1404, USA. Electronic address: monic.roengvoraphoj@hitchcock.org.

RESUMEN / SUMMARY: - Activation of the epidermal growth factor receptor (EGFR) pathway has been implicated in tumorigenesis in non-small cell lung cancer (NSCLC), the most common type of lung cancer. As a result, EGFR has become a key focus for the development of personalized therapy, with several molecular biomarkers having been investigated as potential predictors of response with EGFR tyrosine kinase inhibitors (TKIs) in NSCLC (e.g., EGFR expression, EGFR gene copy gain, and EGFR mutations). Of these, activating mutations in EGFR have thus far given the most consistent results based on the available evidence from preclinical studies and clinical trials. In an attempt to identify patients who are most likely to benefit from treatment with EGFR TKIs, EGFR mutation testing is being increasingly utilized in clinical practice. Currently in the United States, no EGFR TKI or accompanying mutational test is approved for the identification and first-line treatment of patients with advanced NSCLC. However, the first-generation EGFR TKIs, erlotinib and gefitinib, as

well as investigational ErbB family TKIs and EGFR mutation testing methods are being evaluated in this setting. This review will discuss EGFR mutation testing as a biomarker of response to EGFR TKIs and the evolution of EGFR mutational analysis in NSCLC. Completed and ongoing clinical trials evaluating currently available or investigational EGFR TKIs as first-line therapy in molecularly and clinically selected patients with NSCLC, with a focus on trials in patients whose tumors have EGFR mutations, will also be reviewed.

[55]

TÍTULO / TITLE: - TNF-alpha gene promoter polymorphisms and risk of venous thromboembolism in gastrointestinal cancer patients undergoing chemotherapy.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt251](#)

AUTORES / AUTHORS: - Roselli M; Ferroni P; Rolfo C; Peeters M; Palmirotta R; Formica V; Ludovici G; Laudisi A; De Marchis ML; La Farina F; Russo A; Guadagni F

INSTITUCIÓN / INSTITUTION: - Medical Oncology, Department of System Medicine, Tor Vergata Clinical Center, University of Rome 'Tor Vergata', Rome.

RESUMEN / SUMMARY: - BACKGROUND: TNF-alpha has been proposed as a predictive factor for venous thromboembolism (VTE). Genetic polymorphisms could regulate TNF-alpha production. However, the relationship between TNFA gene variants and VTE is not clarified. This study aims to investigate the predictive role of five different TNFA gene promoter SNPs, or their haplotype combination(s), for a first VTE episode in gastrointestinal cancer out-patients treated with chemotherapy. PATIENTS AND METHODS: Serum TNF-alpha levels and TNFA -863C/A, -857C/T, -376G/A, -308G/A and -238G/A gene promoter polymorphisms were retrospectively evaluated in 314 subjects, including 157 controls and 157 Caucasian patients with histologically diagnosed GI cancers beginning chemotherapy delivery (5-fluorouracil either as monotherapy or in combination with platinum compounds or irinotecan). RESULTS: Haplotype analysis showed that a five-loci haplotype (CTGGG haplotype) has higher frequency in GI cancer patients who developed VTE (n = 15) during chemotherapy [odds ratio = 2.7, 95% confidence interval (CI) 1.04-7.11, P = 0.04]. GI patients who remained VTE-free did not differ in CTGGG haplotype frequency from controls. No association was observed between serum TNF-alpha levels and TNFA haplotype, but both were independent predictors of VTE. Approximately 20% of GI cancer patients carrying the CTGGG haplotype developed VTE compared with 4% of the remaining 101 patients (hazard ratio = 5.6, 95% CI 1.8-17.6, P = 0.003). CONCLUSION: These results suggest that TNFA might represent a candidate gene contributing to VTE pathogenesis in GI cancer patients and suggest that VTE risk during

chemotherapy might be genetically identified. Validation studies are needed for translation into clinical practice.

[56]

TÍTULO / TITLE: - Tyrosine kinase inhibitor usage, treatment outcome and prognostic scores in CML: report from the population-based Swedish CML registry.

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

REVISTA / JOURNAL: - Blood. 2013 Jul 10.

- Enlace al texto completo (gratis o de pago) 1182/blood-2013-04-495598

AUTORES / AUTHORS: - Hoglund M; Sandin F; Hellstrom K; Bjoreman M; Bjorkholm M; Brune M; Dreimane A; Ekblom M; Lehmann S; Ljungman P; Malm C; Markevarn B; Myhr-Eriksson K; Ohm L; Olsson-Stromberg U; Sjalander A; Wadenvik H; Simonsson B; Stenke L; Richter J

INSTITUCIÓN / INSTITUTION: - Department of Medical Science and Division of Hematology, University Hospital, Uppsala, Sweden;

RESUMEN / SUMMARY: - Clinical management guidelines on malignant disorders are generally based on data from clinical trials with selected patient cohorts. In Sweden, more than 95% of all patients diagnosed with chronic myeloid leukemia (CML) are reported to the national CML registry, providing unique possibilities to compile population-based information. This report is based on registry data from 2002 - 2010 when a total of 779 patients (m/f: 425/354; median age 60 years) were diagnosed with CML (93% in chronic, 5% accelerated and 2% blastic phase) corresponding to an annual incidence of 0.9/100,000. In 2002, approximately half of the patients received a tyrosine kinase inhibitor (TKI) as initial therapy, a proportion that increased to 94% for younger (<70 years) and 79% for older (>80 years) patients during 2007-2009. With a median follow-up of 61 months, the relative survival at 5 years was close to 1.0 for patients <60, 0.9 for 60-80 but only 0.6 for >80 years. At 12 months, 3% had progressed to accelerated or blastic phase. Sokal, but not EUTOS, high risk score was significantly linked to inferior overall and relative survival. Patients living in university vs. non-university catchment areas were more often receiving TKI upfront but showed comparable survival.

[57]

TÍTULO / TITLE: - Cetuximab plus chemotherapy as first-line treatment for metastatic colorectal cancer: Effect of KRAS mutation on treatment efficacy in Taiwanese patients.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(5):561-7. doi: 10.4149/neo_2013_073.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2013_073](#)

AUTORES / AUTHORS: - Chen MC; Chiang FF; Wang HM

RESUMEN / SUMMARY: - Cetuximab, either alone or in combination with chemotherapy, is approved for treatment of patients with metastatic colorectal cancer (mCRC). We reviewed retrospectively records of 50 patients with mCRC from a single center in Taiwan. All patients had ECOG performance status grade 2, histological diagnosis of advanced CRC based on RECIST criteria, and were given at least three cycles of chemotherapy plus cetuximab. We compared the effectiveness of therapy in patients with wild-type and mutant KRAS genes, assessed the overall response (OR) rate of patients with locally advanced or metastatic non-resectable CRC, and assessed the progression-free survival (PFS) time. The ten patients with KRAS mutations had poorer response rates than the 40 patients with the wild-type KRAS gene. Patients with the wild-type and mutant genes had similar progression free survival (PFS) status and median time to PFS. The median overall survival time was significantly greater in patients with the wild-type gene than in those with the mutant gene (28.77 +/- 6.43 months vs. 15.13 +/- 0.50 months, p=0.014). Taiwanese patients with mCRC respond better to cetuximab plus chemotherapy regime if their tumors have the wild-type KRAS gene. **Keywords:** cetuximab, colorectal cancer, irinotecan, KRAS, oxaliplatin, 5-fluorouracil.

[58]

TÍTULO / TITLE: - Association of ERCC1-C118T and -C8092A polymorphisms with lung cancer risk and survival of advanced-stage non-small cell lung cancer patients receiving platinum-based chemotherapy: A pooled analysis based on 39 reports.

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

REVISTA / JOURNAL: - Gene. 2013 Sep 10;526(2):265-74. doi: 10.1016/j.gene.2013.05.021. Epub 2013 May 30.

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

[1016/j.gene.2013.05.021](#)

AUTORES / AUTHORS: - Xu TP; Shen H; Liu LX; Shu YQ

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: - The published data on the predictive role of ERCC1 polymorphisms in lung cancer risk and survival of patients with advanced non-small cell lung cancer (NSCLC) receiving platinum-based chemotherapy remains inconsistent. The aim of this meta-analysis was to determine the role of ERCC1 gene polymorphisms (C118T and C8092A) in this clinical situation. Eligible studies were included and assessed for quality using multiple search strategies. Thirty-nine published papers involving 9615 cases (4606 with Stage III/IV disease) and 5542 controls were included in the analysis. Pooled odds

ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI) were used to estimate risk. ERCC1-C118T was associated with lung cancer risk. The OR was 0.90 (95% CI: 0.81-0.99, p=0.043) in an additive genetic model (C allele vs. T allele) and 0.77 (95% CI: 0.63-0.95, p=0.013) in a recessive genetic model (CC/CT vs. TT). The corresponding risk was 0.74 (95% CI: 0.58-0.94, p=0.013) based on a homozygous comparison (CC vs. TT). No significant correlation was found for ERCC1 C8092A and there was no obvious relationship between ERCC1 C118T/C8092A polymorphisms and objective response to platinum-based chemotherapy. Overall survival (OS) of patients with non-small cell lung cancer (NSCLC) receiving platinum-based chemotherapy was significantly related to ERCC1 C118T (HR: 1.29, 95% CI: 1.07-1.56, p=0.007, CT/TT vs. CC). There was no relationship between ERCC1 C8092A and survival (HR: 1.32, 95% CI: 0.84-2.10, p=0.23, CA/AA vs. CC). These findings suggest that ERCC1 C118T polymorphisms may serve as a biomarker for lung cancer risk and have prognostic value in patients with advanced non-small cell lung cancer (NSCLC) undergoing platinum-based treatment. Further studies with larger numbers of subjects from a worldwide arena are needed to validate the associations.

[59]

TÍTULO / TITLE: - Remobilization of hematopoietic stem cells with high-dose methotrexate and cytarabine in patients with non-Hodgkin's lymphoma and multiple myeloma after failure to mobilize with chemotherapy and cytokines.

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

REVISTA / JOURNAL: - Transfusion. 2013 Jun 26. doi: 10.1111/trf.12314.

●● Enlace al texto completo (gratis o de pago) [1111/trf.12314](#)

AUTORES / AUTHORS: - Park SJ; Yoon DH; Kim S; Lee K; Park JS; Jang S; Park CJ; Chi HS; Park CS; Huh J; Suh C

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND: High-dose chemotherapy supported by autologous stem cell transplantation is an effective treatment for patients with relapsed or refractory non-Hodgkin's lymphomas (NHLs) and fit patients with multiple myeloma (MM). However, failure rates of hematopoietic stem cell mobilization are estimated to be between 5 and 30%, respectively. Thus, we investigated the efficacy of the combination chemotherapy of high-dose methotrexate (MTX) and cytarabine with granulocyte-colony-stimulating factor (G-CSF) as a remobilization method in those who failed a prior mobilization and collection with chemotherapy and G-CSF. STUDY DESIGN AND METHODS: Mobilization failure was defined as a collection of fewer than 5 x 10⁶ CD34+

cells after three to five apheresis procedures. MTX (3500 mg/m² in a 120-min infusion) on Day 1 and cytarabine (3000 mg/m² infusion for 120 min) on Day 4 and Day 5 were followed by G-CSF (10 µg/kg daily). RESULTS: A total of eight patients (six NHL and two MM; median age, 55 years) who had failed in prior mobilization with conventional chemotherapy and G-CSF underwent the second mobilization as described in the method. Successful collection of CD34+ cells (> 5 x 10⁶ /kg) was achieved in six patients (75%) with three to five apheresis procedures. The total yield of CD34+ cells/kg body weight was 6.28 x 10⁶ /kg (median; range, 1.53 x 10⁶ -10.09 x 10⁶ /kg). CONCLUSIONS: This preliminary result warrants further investigation of high-dose MTX and cytarabine plus G-CSF as a means to remobilize stem cells in those with prior failure to mobilize stem cells with chemotherapy and G-CSF.

[60]

TÍTULO / TITLE: - EGFR tyrosine kinase inhibitors beyond focal progression obtain a prolonged disease control in patients with advanced adenocarcinoma of the lung.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Jun 26. pii: S0169-5002(13)00252-3. doi: 10.1016/j.lungcan.2013.05.019.

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

[1016/j.lungcan.2013.05.019](#)

AUTORES / AUTHORS: - Conforti F; Catania C; Toffalorio F; Duca M; Spitaleri G; Barberis M; Noberasco C; Delmonte A; Santarpia M; Lazzari C; De Pas TM

INSTITUCIÓN / INSTITUTION: - Thoracic and Sarcoma Oncology Unit, Division of New Drug Development and Clinical Pharmacology, Medical Oncology Department, European Institute of Oncology, Milano, Italy. Electronic address: fabcon_84@yahoo.it.

RESUMEN / SUMMARY: - INTRODUCTION: Recent data show that EGFR pathway and its inhibition maintain their role after progression of disease during EGFR TKI therapy in NSCLCs. We conducted a retrospective study with the aim of evaluating efficacy and feasibility of prosecution of EGFR TKI therapy beyond focal progression associated to locoregional radiotherapy. METHODS: We retrospectively analyzed the data of all NSCLC patients treated with EGFR TKIs in our institution from 2004 to 2012. We included in the analysis patients that after a focal disease progression, meant as a single lesion RECIST progression, have been treated with definitive locoregional radiotherapy, associated to continuation of EGFR TKI therapy until further progression. RESULTS: 15 out of 147 patients (10%) satisfied inclusion criteria. The median progression free survival, measured from the date of focal progression until further progression of disease or death by any cause, was 10,9 months (range 3-32 months). The corresponding 6 and 12 months PFS rates were 73% and 33%, respectively. CONCLUSION: The longer disease control observed in our

patients suggests that continuation of EGFR TKI beyond focal progression associated to a locoregional treatment is an efficacious therapeutic strategy.

[61]

TÍTULO / TITLE: - Cyclophosphamide induces a type I interferon-associated sterile inflammatory response signature in cancer patients' blood cells: implications for cancer chemoimmunotherapy.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4249-61. doi: 10.1158/1078-0432.CCR-12-3666. Epub 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3666](#)

AUTORES / AUTHORS: - Moschella F; Torelli GF; Valentini M; Urbani F; Buccione C; Petrucci MT; Natalino F; Belardelli F; Foa R; Proietti E

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Department of Hematology Oncology and Molecular Medicine, Istituto Superiore di Sanita; and Department of Cellular Biotechnologies and Hematology, Azienda Policlinico Umberto I, Sapienza University, Rome, Italy.

RESUMEN / SUMMARY: - **PURPOSE:** Certain chemotherapeutics, particularly cyclophosphamide, can enhance the antitumor efficacy of immunotherapy. A better understanding of the cellular and molecular basis of cyclophosphamide-mediated immunomodulation is needed to improve the efficacy of chemoimmunotherapy. **EXPERIMENTAL DESIGN:** Transcript profiling and flow cytometry were used to explore cyclophosphamide-induced immunoadjuvanticity in patients with hematologic malignancies. **RESULTS:** A single high-dose treatment rapidly (1-2 days) induced peripheral blood mononuclear cell (PBMC) transcriptional modulation, leading to reduction of cell-cycle and biosynthetic/metabolic processes and augmentation of DNA damage and cell death pathways (p53 signaling pathway), death-related scavenger receptors, antigen processing/presentation mediators, T-cell activation markers and, noticeably, a type I IFN (IFN-I) signature (OAS1, CXCL10, BAFF, IFITM2, IFI6, IRF5, IRF7, STAT2, UBE2L6, UNC93B1, ISG20L1, TYK2). Moreover, IFN-I-induced proinflammatory mediators (CXCL10, CCL2, IL-8, and BAFF) were increased in patients' plasma. Accordingly, cyclophosphamide induced the expansion/activation of CD14(+)CD16(+) monocytes, of HLA-DR(+), IL-8RA(+), and MARCO(+) monocytes/dendritic cells, and of CD69(+), OX40(+), and IL-8RA(+) lymphocytes. **CONCLUSIONS:** Altogether, these data identify the cyclophosphamide-induced immunomodulatory factors in humans and indicate that preconditioning chemotherapy may stimulate immunity as a consequence of danger perception associated with blood cell death, through p53 and IFN-I-related mechanisms. Clin Cancer Res; 19(15); 4249-61. ©2013 AACR.

[62]

TÍTULO / TITLE: - Regulation of E2F1 by the von Hippel-Lindau tumour suppressor protein predicts survival in renal cell cancer patients.

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

REVISTA / JOURNAL: - J Pathol. 2013 Sep;231(1):117-29. doi: 10.1002/path.4219.

●● Enlace al texto completo (gratis o de pago) [1002/path.4219](#)

AUTORES / AUTHORS: - Mans DA; Vermaat JS; Weijts BG; van Rooijen E; van Rieuwijk J; Boldt K; Daenen LG; van der Groep P; Rowland BD; Jans JJ; Roepman R; Voest EE; van Diest PJ; Verhaar MC; de Bruin A; Giles RH

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University Medical Centre Utrecht, The Netherlands; Department of Human Genetics, Radboud University Nijmegen Medical Centre, The Netherlands; Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, The Netherlands.

RESUMEN / SUMMARY: - Biallelic mutations of the von Hippel-Lindau (VHL) gene are the most common cause of sporadic and inherited renal cell carcinoma (RCC). Loss of VHL has been reported to affect cell proliferation by deregulating cell cycle-associated proteins. We report that the VHL gene product (pVHL) inhibits E2F1 expression at both mRNA and protein level in zebrafish and human RCC cells, while loss of VHL increases E2F1 expression in patient kidney tumour tissue and RCC cells, resulting in a delay of cell cycle progression. RCCs from von Hippel-Lindau patients with known germline VHL mutations express significantly more E2F1 compared to sporadic RCCs with either clear-cell (cc) or non-cc histology. Analysis of 138 primary RCCs reveals that E2F1 expression is significantly higher in tumours with a diameter ≤ 7 cm and with a favourable American Joint Committee on Cancer (AJCC) stage. The expression of E2F1 in RCC significantly correlates with p27 expression, suggesting that increased expression of E2F1 in RCC induces tumour cell senescence via p27. Cox regression analysis shows significant prediction of E2F1 expression for disease-free survival and overall survival, implying that E2F1 expression in kidney tumour is a novel prognostic factor for patients with RCC. Copyright © 2013 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

[63]

TÍTULO / TITLE: - Prediction of Disease-free Survival in Hepatocellular Carcinoma by Gene Expression Profiling.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3070-](#)

[y](#)

AUTORES / AUTHORS: - Lim HY; Sohn I; Deng S; Lee J; Jung SH; Mao M; Xu J; Wang K; Shi S; Joh JW; Choi YL; Park CK

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - BACKGROUND: Progression of hepatocellular carcinoma (HCC) often leads to vascular invasion and intrahepatic metastasis, which correlate with recurrence after surgical treatment and poor prognosis. The molecular prognostic model that could be applied to the HCC patient population in general is needed for effectively predicting disease-free survival (DFS). METHODS: A cohort of 286 HCC patients from South Korea and a second cohort of 83 patients from Hong Kong, China, were used as training and validation sets, respectively. RNA extracted from both tumor and adjacent nontumor liver tissues was subjected to microarray gene expression profiling. DFS was the primary clinical end point. Gradient lasso algorithm was used to build prognostic signatures. RESULTS: High-quality gene expression profiles were obtained from 240 tumors and 193 adjacent nontumor liver tissues from the training set. Sets of 30 and 23 gene-based DFS signatures were developed from gene expression profiles of tumor and adjacent nontumor liver, respectively. DFS gene signature of tumor was significantly associated with DFS in an independent validation set of 83 tumors ($P = 0.002$). DFS gene signature of nontumor liver was not significantly associated with DFS in the validation set ($P = 0.827$). Multivariate analysis in the validation set showed that DFS gene signature of tumor was an independent predictor of shorter DFS ($P = 0.018$). CONCLUSIONS: We developed and validated survival gene signatures of tumor to successfully predict the length of DFS in HCC patients after surgical resection.

[64]

TÍTULO / TITLE: - Polymorphisms of Interferon Gamma Gene and Risk of Hepatocellular Carcinoma in Korean Patients with Chronic Hepatitis B Viral Infection.

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

REVISTA / JOURNAL: - Hepatogastroenterology. 2013 Jun 27;60(125):1117-1120. doi: 10.5754/hge11333.

●● Enlace al texto completo (gratis o de pago) [5754/hge11333](#)

AUTORES / AUTHORS: - Kim HJ; Chung1 JH; Shin HP; Jeon JW; Park JJ; Cha JM; Joo KR; Lee JI

RESUMEN / SUMMARY: - Backgrounds/Aims: Increasing evidence supports the contribution of the pro-/anti-inflammatory cytokine balance and genetic factors to hepatocellular carcinoma (HCC). Here, we investigated whether genetic interferon gamma polymorphisms were associated with HCC in Korean patients with chronic hepatitis B. Methodology: We genotyped a single nucleotide

polymorphism (SNP, rs2430561, +874^a/T) and a microsatellite (rs3138557, (CA)_n repeat), located in the first intron of the interferon gamma gene, by direct sequencing and the gene scan method. A population-based case-control study of HCC was conducted and included 170 patients with chronic hepatitis and HCC, and 171 with chronic hepatitis B patients without hepatocellular carcinoma in a Korean population. Results: Genotype and allele distributions of the interferon gamma gene SNP were associated with HCC. The frequencies of the AA genotype and the A allele were significantly increased in hepatocellular carcinoma subjects (p<0.05). Combined analysis using the genotype of rs2430561 and the number of microsatellites revealed that the frequencies of AT-CA12 and TT-CA12 increased significantly in hepatocellular carcinoma subjects (p<0.0001). Conclusions: Our results suggest that the interferon gamma gene may be a susceptibility gene and a risk factor for HCC in the Korean population.

[65]

TÍTULO / TITLE: - High early death rate in elderly patients with acute promyelocytic leukemia treated with all-trans retinoic acid combined chemotherapy.

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

REVISTA / JOURNAL: - Int J Hematol. 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) 1007/s12185-013-1390-0

AUTORES / AUTHORS: - Imagawa J; Harada Y; Shimomura T; Tanaka H; Okikawa Y; Harada H

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8553, Japan.

[66]

TÍTULO / TITLE: - Phase I Study of BIIB028, a selective heat shock protein 90 inhibitor, in patients with refractory metastatic or locally advanced solid tumors.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 19.

●● Enlace al texto completo (gratis o de pago) 1158/1078-0432.CCR-13-0477

AUTORES / AUTHORS: - Hong DS; Said R; Falchook GS; Naing A; Moulder SL; Tsimberidou AM; Galluppi G; Dakappagari N; Storgard C; Kurzrock R; Rosen LS

INSTITUCIÓN / INSTITUTION: - Investigational Cancer Therapeutics, UT MD Anderson Cancer Center.

RESUMEN / SUMMARY: - PURPOSE: Heat shock protein 90 (Hsp90) is a ubiquitous molecular chaperone involved in protein folding, activation, and assembly, including key mediators of signal transduction, cell cycle control, and transcriptional regulation. We conducted a phase I dose-finding and pharmacokinetic/pharmacodynamic study of BIIB028, a prodrug designed to inhibit Hsp90 activity. EXPERIMENTAL DESIGN: Patients with advanced solid tumors were enrolled and received escalating doses of BIIB028 intravenously twice a week in 21-day cycles (3+3 design). Response was evaluated after 2 cycles. RESULTS: Forty-one patients received doses of 6 to 192 mg/m². The maximum tolerated dose was 144 mg/m². Dose-limiting toxicities were syncope (n=1) and fatigue (n=1). Common toxicities at least possibly related to drug were grade 1-2, including fatigue (46%), diarrhea (44%), nausea (44%), vomiting (29%), hot flushes (29%) and abnormal dreams (17%). The concentration-time curves for Day 1 and Day 18 for both prodrug and active metabolite (CF2772) showed a negligible difference. There was a dose-dependent increase in plasma exposure for BIIB028 (CF3647) and CF2772 with plasma half-life of 0.5 and 2.1 hours, respectively. Pharmacodynamic analyses demonstrated significant increases in Hsp70 in peripheral blood mononuclear cells and significantly decreased circulating human epidermal growth factor receptor 2- extracellular domain in all patients who received BIIB028 at dose levels ≥ 48 mg/m². Stable disease for at least 8 cycles (24 weeks) was achieved in 5 (12%) patients (6, 6, 8, 12.5 and 19 months). CONCLUSIONS: BIIB028 is a well-tolerated molecule that demonstrated target impact and was associated with prolonged stable disease in 2 patients.

[67]

TÍTULO / TITLE: - Predicting Postoperative Morbidity Following Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CS+HIPEC) with Preoperative FACT-C (Functional Assessment of Cancer Therapy) and Patient-Rated Performance Status.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 8.

- Enlace al texto completo (gratis o de pago) [1245/s10434-013-3049-](#)

[8](#)

AUTORES / AUTHORS: - Ihemelandu CU; McQuellon R; Shen P; Stewart JH; Votanopoulos K; Levine EA

INSTITUCIÓN / INSTITUTION: - Section of Surgical Oncology, Department of General Surgery, Wake Forest School of Medicine, Winston-Salem, NC, USA, emeka_ihemelandu@hotmail.com.

RESUMEN / SUMMARY: - BACKGROUND: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS+HIPEC) is associated with significant perioperative morbidity. One goal of our ongoing patient-reported health-related quality of life (HRQoL) program is to describe the prognostic

value of HRQoL measures for predicting postoperative morbidity and mortality following CS+HIPEC. METHODS: A retrospective analysis of a prospectively collected clinical database for all patients treated for peritoneal carcinomatosis and who participated in our patient-reported HRQoL program from 2001 to 2011 was done. Patients completed the Functional Assessment of Cancer Therapy questionnaire plus the colon symptom subscale, in addition to the Eastern Cooperative Oncology Group (ECOG) performance status rating prior to CS+HIPEC. The trial outcome index (TOI), a specific measure of function, symptoms, and physical well being of the patient, was analyzed. The TOI is a combination of the physical and functional well being subscales + the colon-specific subscale of the FACT-C. RESULTS: Of 855 patients, 387 (45.2 %) participated in the HRQoL trials. Mean age was 53.3 years, and 213 (55 %) were female versus 174 (45 %) males. There were 240 patients (62 %) who had a complication versus 147 (38 %) who had no complication. A 30-day mortality rate of 7.7 % (30) was documented. Patients who suffered a 30-day postoperative mortality demonstrated a lower mean preoperative score in the FACT-C TOI 52.7 versus 61.7; $P < 0.001$. Independent predictors of 30-day mortality on multivariate analysis included TOI (0.05), age (0.001), and smoking (0.001). Patients with a higher TOI score were less likely to suffer a mortality (95 % CI 0.9-1.0, $P = 0.05$). Patients with a higher emotional well being (EWB) score were less likely to suffer a complication 0.9 (95 % CI 0.87-1.0, $P = 0.04$). Other independent predictors of postoperative morbidity included diabetic status ($P = 0.05$), ECOG performance status (0.001), and gender (0.02). CONCLUSIONS: Preoperative HRQoL, as measured by FACT-C and ECOG performance status and added to traditional factors, helps predict postoperative morbidity and mortality following CS+HIPEC.

[68]

TÍTULO / TITLE: - The Use of O-(2-18F-Fluoroethyl)-L-Tyrosine PET for Treatment Management of Bevacizumab and Irinotecan in Patients with Recurrent High-Grade Glioma: A Cost-Effectiveness Analysis.

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

REVISTA / JOURNAL: - J Nucl Med. 2013 Aug;54(8):1217-22. doi: 10.2967/jnumed.113.120089. Epub 2013 Jun 19.

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

[2967/jnumed.113.120089](#)

AUTORES / AUTHORS: - Heinzl A; Muller D; Langen KJ; Blaum M; Verburg FA; Mottaghy FM; Galldiks N

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, University of Aachen, Aachen, Germany.

RESUMEN / SUMMARY: - To date, the use of structural MR imaging (including contrast-enhanced and T2-weighted or fluid-attenuated inversion recovery-weighted images) is the standard method to diagnose tumor progression and to

assess antiangiogenic treatment effects. However, several studies have suggested that O-(2-(18)F-fluoroethyl)-l-tyrosine ((18)F-FET) PET adds valuable clinical information to the information derived from structural MR imaging alone. We evaluated the effectiveness and cost-effectiveness of the addition of (18)F-FET PET to structural MR imaging for the management of treatment with bevacizumab and irinotecan (BEV/IR) in patients with recurrent high-grade glioma compared with MR imaging alone from the perspective of the German Statutory Health Insurance. METHODS: To evaluate the incremental cost-effectiveness of the additional use of (18)F-FET PET, a decision tree model was used. Effectiveness of (18)F-FET PET was defined as correct identification of both tumor progression before BEV/IR treatment initiation and BEV/IR treatment response and was evaluated for the combination of (18)F-FET PET and MR imaging compared with MR imaging alone. Costs were estimated for a baseline scenario and for a more expensive scenario. The robustness of the results was tested using deterministic and probabilistic sensitivity analyses. RESULTS: The use of (18)F-FET PET resulted in a number needed to diagnose of 2.4, that is, 3 additional patients have to be diagnosed to avoid 1 wrong diagnosis. The incremental cost-effectiveness ratio of (18)F-FET PET/MR imaging compared with MR imaging alone was euro5,725 (euro1 approximately \$1.30) for the baseline scenario and euro8,145 for the more expensive scenario per additional correct diagnosis. The probabilistic sensitivity analysis confirmed the robustness of the results. CONCLUSION: The model suggests that the additional use of (18)F-FET PET in the management of patients with recurrent high-grade glioma treated with BEV/IR may be cost-effective. Integration of (18)F-FET PET has the potential to avoid overtreatment and corresponding costs, as well as unnecessary side effects to the patient.

[69]

TÍTULO / TITLE: - The Src and c-Kit kinase inhibitor dasatinib enhances p53-mediated targeting of human acute myeloid leukemia stem cell by chemotherapeutic agents.

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

REVISTA / JOURNAL: - Blood. 2013 Jul 29.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2012-11-466425](#)

AUTORES / AUTHORS: - Dos Santos C; McDonald T; Ho YW; Liu H; Lin A; Forman SJ; Kuo YH; Bhatia R

INSTITUCIÓN / INSTITUTION: - Division of Hematopoietic Stem Cell and Leukemia Research, City of Hope National Medical Center, Duarte, CA, United States;

RESUMEN / SUMMARY: - The SRC Family Kinases (SFKs) and the receptor tyrosine kinase c-Kit, are activated in human acute myeloid leukemia (AML) cells. We show here that the SFKs LYN, HCK or FGR are overexpressed and

activated in AML progenitor cells. Treatment with the SFK and c-KIT inhibitor dasatinib selectively inhibits human AML stem/progenitor cell growth in vitro. Importantly, dasatinib markedly increases the elimination of AML stem cells capable of engrafting immunodeficient mice by chemotherapeutic agents. In vivo dasatinib treatment enhances chemotherapy induced targeting of primary murine AML stem cells capable of regenerating leukemia in secondary recipients. Our studies suggest that enhanced targeting of AML cells by the combination of dasatinib with daunorubicin (DNR) may be related to inhibition of AKT mediated HDM2 phosphorylation, resulting in enhanced p53 activity in AML cells. Combined treatment using dasatinib and chemotherapy provides a novel approach to increase p53 activity and enhance targeting of AML stem cells.

[70]

TÍTULO / TITLE: - Reciprocal expression of the endocytic protein HIP1R and its repressor FOXP1 predicts outcome in R-CHOP-treated diffuse large B-cell lymphoma patients.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jul 25. doi: 10.1038/leu.2013.224.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.224](#)

AUTORES / AUTHORS: - Wong KK; Gascoyne DM; Brown PJ; Soilleux EJ; Snell C; Chen H; Lyne L; Lawrie CH; Gascoyne RD; Pedersen LM; Moller MB; Pulford K; Murphy D; Green TM; Banham AH

INSTITUCIÓN / INSTITUTION: - 1] NDCLS, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK [2] Department of Immunology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia.

RESUMEN / SUMMARY: - We previously identified autoantibodies to the endocytic-associated protein Huntingtin interacting protein 1-related (HIP1R) in diffuse large B-cell lymphoma (DLBCL) patients. HIP1R regulates internalization of cell surface receptors via endocytosis, a process relevant to many therapeutic strategies including CD20 targeting with rituximab. In this study, we characterized HIP1R expression patterns, investigated a mechanism of transcriptional regulation and its clinical relevance in DLBCL patients treated with immunochemotherapy (R-CHOP). HIP1R was preferentially expressed in germinal center-derived (GCB)-DLBCL ($P < 0.0001$) and inversely correlated with the activated B-cell-like (ABC-DLBCL) associated transcription factor, FOXP1. HIP1R was confirmed as a direct FOXP1 target gene in ABC-DLBCL by FOXP1-targeted silencing and chromatin immunoprecipitation. Lower HIP1R protein expression ($\leq 10\%$ tumoral positivity) significantly correlated with inferior overall (OS, $P = 0.0003$) and progression-free (PFS, $P = 0.0148$) survival in R-CHOP-treated DLBCL patients ($n = 157$). Reciprocal expression with $\geq 70\%$ FOXP1 positivity defined FOXP1^{hi}/HIP1R^{lo} patients with particularly

poor outcome (OS, $P=0.0001$; PFS, $P=0.0016$). In an independent R-CHOP-treated DLBCL ($n=233$) microarray dataset, patients with transcript expression in lower quartile HIP1R and FOXP1^{hi}/HIP1R^{lo} subgroups exhibited worse OS, $P=0.0044$ and $P=0.0004$, respectively. HIP1R repression by FOXP1 is strongly associated with poor outcome, thus further understanding of FOXP1-HIP1R and/or endocytic signaling pathways might give rise to novel therapeutic options for DLBCL. Leukemia accepted article preview online, 25 July 2013.
doi:10.1038/leu.2013.224.

[71]

TÍTULO / TITLE: - SDF-1/CXCR4 signaling induces apoptosis in acute myeloid leukemia cells via regulation of the Bcl-2 family members Bcl-XL, Noxa, and Bak.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jun 24.

●● [Enlace al texto completo \(gratis o de pago\) 1074/jbc.M113.449926](#)

AUTORES / AUTHORS: - Kremer KN; Peterson KL; Schneider PA; Meng XW; Dai H; Hess AD; Smith BD; Rodriguez-Ramirez C; Karp JE; Kaufmann SH; Hedin KE

INSTITUCIÓN / INSTITUTION: - Mayo Clinic College of Medicine, United States;

RESUMEN / SUMMARY: - The CXCR4 chemokine receptor promotes survival of many different cell types. Here, we describe a previously unsuspected role for CXCR4 as a potent inducer of apoptosis in acute myeloid leukemia (AML) cell lines and a subset of clinical AML samples. We show that SDF-1, the sole ligand for CXCR4, induces the expected migration and ERK activation in the KG1a AML cell line transiently overexpressing CXCR4, but ERK activation did not lead to survival. Instead, SDF-1 treatment led via a CXCR4-dependent mechanism to apoptosis, as evidenced by increased annexin V staining, condensation of chromatin, and cleavage of both procaspase-3 and PARP. This SDF-1-induced death pathway was partially inhibited by hypoxia, which is often found in the bone marrow of AML patients. SDF-1-induced apoptosis was inhibited by dominant negative procaspase-9 but not by inhibition of caspase-8 activation, implicating the intrinsic apoptotic pathway. Further analysis showed that this pathway was activated by multiple mechanisms, including upregulation of Bak at the level of mRNA and protein, stabilization of the Bak activator Noxa, and downregulation of anti-apoptotic Bcl-XL. Furthermore, adjusting expression levels of Bak, Bcl-XL, or Noxa individually altered the level of apoptosis in AML cells, suggesting that the combined modulation of these family members by SDF-1 coordinates their interplay to produce apoptosis. Thus, rather than mediating survival, SDF-1 may be a means to induce apoptosis of CXCR4-expressing AML cells directly in the SDF-1-rich bone marrow microenvironment if the survival cues of the bone marrow are disrupted.

[72]

TÍTULO / TITLE: - Association between Phosphorylated AMP-Activated Protein Kinase and MAPK3/1 Expression and Prognosis for Patients with Gastric Cancer.

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

REVISTA / JOURNAL: - Oncology. 2013 Jul 16;85(2):78-85.

●● Enlace al texto completo (gratis o de pago) [1159/000351234](#)

AUTORES / AUTHORS: - Kim JG; Lee SJ; Chae YS; Kang BW; Lee YJ; Oh SY; Kim MC; Kim KH; Kim SJ

INSTITUCIÓN / INSTITUTION: - Center for Oncology/Hematology, Kyungpook National University Medical Center, Kyungpook National University School of Medicine, Daegu, Korea.

RESUMEN / SUMMARY: - Objectives: Phosphorylated AMP-activated protein kinase (pAMPK) plays a central role in cellular metabolic sensing and energy balance homeostasis, and interacts with various pathways [e.g., TP53, mTOR, NUA2 (sucrose nonfermenting-like kinase), MAPK3/1 (ERK) and PDK]. Therefore, the present study analyzed the expression of pAMPK, NUA2, MAPK3/1 and PDK-1 and their effect on the survival of patients with resected gastric cancer. Methods: A total of 621 patients with gastric adenocarcinoma surgically resected with curative intent were enrolled in the study. Immunohistochemical staining for pAMPK, NUA2, MAPK3/1 and PDK-1 was performed using tissue microarrays of surgical specimens of gastric cancer tissue. Results: Positive pAMPK, NUA2, MAPK3/1 and PDK-1 expression was observed in 379 (61.0%), 257 (41.4%), 327 (52.7%) and 67 (10.8%) cases, respectively. Multivariate survival analysis showed a significantly better survival for the patients with positive pAMPK or MAPK3/1 expression than for the patients with a negative expression [pAMPK: disease-free survival (DFS), hazard ratio (HR) = 0.750, 95% confidence interval (CI) = 0.568-0.970, p = 0.030; MAPK3/1: DFS, HR = 0.692, 95% CI = 0.720-0.974, p = 0.021), while NUA2 or PDK-1 expression had no effect on survival. Conclusion: pAMPK or MAPK3/1 expression was found to be an independent prognostic marker for patients with resected gastric cancer.

[73]

TÍTULO / TITLE: - Development and validation of a prognostic model in patients with metastatic renal cell carcinoma treated with sunitinib: a European collaboration.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 23;109(2):332-41. doi: 10.1038/bjc.2013.341. Epub 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.341](#)

AUTORES / AUTHORS: - Bamias A; Tzannis K; Beuselinck B; Oudard S; Escudier B; Diosynopoulos D; Papazisis K; Lang H; Wolter P; de Guillebon E;

Stravodimos K; Chrisofos M; Fountzilas G; Elaidi RT; Dimopoulos MA; Bamia C

INSTITUCIÓN / INSTITUTION: - Department of Clinical Therapeutics, University of Athens, Athens, Greece.

RESUMEN / SUMMARY: - Background:Accurate prediction of outcome for metastatic renal cell carcinoma (mRCC) patients receiving targeted therapy is essential. Most of the available models have been developed in patients treated with cytokines, while most of them are fairly complex, including at least five factors. We developed and externally validated a simple model for overall survival (OS) in mRCC. We also studied the recently validated International Database Consortium (IDC) model in our data sets.Methods:The development cohort included 170 mRCC patients treated with sunitinib. The final prognostic model was selected by uni- and multivariate Cox regression analyses. Risk groups were defined by the number of risk factors and by the 25th and 75th percentiles of the model's prognostic index distribution. The model was validated using an independent data set of 266 mRCC patients (validation cohort) treated with the same agent.Results:Eastern Co-operative Oncology Group (ECOG) performance status (PS), time from diagnosis of RCC and number of metastatic sites were included in the final model. Median OS of patients with 1, 2 and 3 risk factors were: 24.7, 12.8 and 5.9 months, respectively, whereas median OS was not reached for patients with 0 risk factors. Concordance © index for internal validation was 0.712, whereas C-index for external validation was 0.634, due to differences in survival especially in poor-risk populations between the two cohorts. Predictive performance of the model was improved after recalibration. Application of the mRCC International Database Consortium (IDC) model resulted in a C-index of 0.574 in the development and 0.576 in the validation cohorts (lower than those recently reported for this model). Predictive ability was also improved after recalibration in this analysis. Risk stratification according to IDC model showed more similar outcomes across the development and validation cohorts compared with our model.Conclusion:Our model provides a simple prognostic tool in mRCC patients treated with a targeted agent. It had similar performance with the IDC model, which, however, produced more consistent survival results across the development and validation cohorts. The predictive ability of both models was lower than that suggested by internal validation (our model) or recent published data (IDC model), due to differences between observed and predicted survival among intermediate and poor-risk patients. Our results highlight the importance of external validation and the need for further refinement of existing prognostic models.

[74]

TÍTULO / TITLE: - Microsatellite Instability and BRAF Mutation Testing in Colorectal Cancer Prognostication.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Aug 7;105(15):1151-6. doi: 10.1093/jnci/djt173. Epub 2013 Jul 22.

●● [Enlace al texto completo \(gratis o de pago\) 1093/jnci/djt173](#)

AUTORES / AUTHORS: - Lochhead P; Kuchiba A; Imamura Y; Liao X; Yamauchi M; Nishihara R; Qian ZR; Morikawa T; Shen J; Meyerhardt JA; Fuchs CS; Ogino S

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA (PL, AK, YI, XL, MY, RN, ZRQ, TM, JAM, CSF, SO); Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK (PL); Department of Pathology (JS, SO) and Channing Division of Network Medicine, Department of Medicine (CSF), Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Department of Epidemiology, Harvard School of Public Health, Boston, MA (SO).

RESUMEN / SUMMARY: - BRAF mutation in colorectal cancer is associated with microsatellite instability (MSI) through its relationship with high-level CpG island methylator phenotype (CIMP) and MLH1 promoter methylation. MSI and BRAF mutation analyses are routinely used for familial cancer risk assessment. To clarify clinical outcome associations of combined MSI/BRAF subgroups, we investigated survival in 1253 rectal and colon cancer patients within the Nurses' Health Study and Health Professionals Follow-up Study with available data on clinical and other molecular features, including CIMP, LINE-1 hypomethylation, and KRAS and PIK3CA mutations. Compared with the majority subtype of microsatellite stable (MSS)/BRAF-wild-type, MSS/BRAF-mutant, MSI-high/BRAF-mutant, and MSI-high/BRAF-wild-type subtypes showed multivariable colorectal cancer-specific mortality hazard ratios of 1.60 (95% confidence interval [CI] = 1.12 to 2.28; P = .009), 0.48 (95% CI = 0.27 to 0.87; P = .02), and 0.25 (95% CI = 0.12 to 0.52; P < .001), respectively. No evidence existed for a differential prognostic role of BRAF mutation by MSI status (P interaction > .50). Combined BRAF/MSI status in colorectal cancer is a tumor molecular biomarker for prognostic risk stratification.

PTPTPTP - Journal Article

[75]

TÍTULO / TITLE: - High dose cytarabine with rituximab is not enough in first-line treatment of mantle cell lymphoma with high proliferation - Early closure of the Nordic Lymphoma Group MCL5 Trial.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 22.

- Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.825906](https://doi.org/10.1073/pnas.1310230110)

AUTORES / AUTHORS: - Laurell A; Kolstad A; Jerkeman M; Raty R; Geisler CH

[76]

TÍTULO / TITLE: - Myc and mTOR converge on a common node in protein synthesis control that confers synthetic lethality in Myc-driven cancers.

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

REVISTA / JOURNAL: - Proc Natl Acad Sci U S A. 2013 Jul 16;110(29):11988-93. doi: 10.1073/pnas.1310230110. Epub 2013 Jun 26.

- Enlace al texto completo (gratis o de pago) [1073/pnas.1310230110](https://doi.org/10.1073/pnas.1310230110)

AUTORES / AUTHORS: - Pourdehnad M; Truitt ML; Siddiqi IN; Ducker GS; Shokat KM; Ruggero D

INSTITUCIÓN / INSTITUTION: - School of Medicine and Department of Urology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94158.

RESUMEN / SUMMARY: - Myc is one of the most commonly deregulated oncogenes in human cancer, yet therapies directly targeting Myc hyperactivation are not presently available in the clinic. The evolutionarily conserved function of Myc in modulating protein synthesis control is critical to the Myc oncogenic program. Indeed, enhancing the protein synthesis capacity of cancer cells directly contributes to their survival, proliferation, and genome instability. Therefore, inhibiting enhanced protein synthesis may represent a highly relevant strategy for the treatment of Myc-dependent human cancers. However, components of the translation machinery that can be exploited as therapeutic targets for Myc-driven cancers remain poorly defined. Here, we uncover a surprising and important functional link between Myc and mammalian target of rapamycin (mTOR)-dependent phosphorylation of eukaryotic translation initiation factor 4E binding protein-1 (4EBP1), a master regulator of protein synthesis control. Using a pharmacogenetic approach, we find that mTOR-dependent phosphorylation of 4EBP1 is required for cancer cell survival in Myc-dependent tumor initiation and maintenance. We further show that a clinical mTOR active site inhibitor, which is capable of blocking mTOR-dependent 4EBP1 phosphorylation, has remarkable therapeutic efficacy in Myc-driven hematological cancers. Additionally, we demonstrate the clinical implications of these results by delineating a significant link between Myc and mTOR-dependent phosphorylation of 4EBP1 and therapeutic response in human lymphomas. Together, these findings reveal that an important mTOR substrate is found hyperactivated downstream of Myc oncogenic activity to promote tumor survival and confers synthetic lethality, thereby revealing a unique therapeutic approach to render Myc druggable in the clinic.

[77]

TÍTULO / TITLE: - 3'-Deoxy-3'-18F-Fluorothymidine PET for the Early Prediction of Response to Leucovorin, 5-Fluorouracil, and Oxaliplatin Therapy in Patients with Metastatic Colorectal Cancer.

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

REVISTA / JOURNAL: - J Nucl Med. 2013 Aug;54(8):1209-16. doi: 10.2967/jnumed.112.117010. Epub 2013 Jun 26.

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

[2967/jnumed.112.117010](#)

AUTORES / AUTHORS: - Hong YS; Kim HO; Kim KP; Lee JL; Kim HJ; Lee SJ; Lee SJ; Oh SJ; Kim JS; Ryu JS; Moon DH; Kim TW

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

RESUMEN / SUMMARY: - The aim of this study was to evaluate 3'-deoxy-3'-(18)F-fluorothymidine ((18)F-FLT) PET for early prediction of the standard anatomic response and survival outcomes in patients with metastatic colorectal cancer (mCRC) receiving leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX). **METHODS:** The main eligibility criteria included histologically confirmed mCRC, ≥ 1 extrahepatic measurable lesions, and no prior chemotherapy in a metastatic setting. Chemotherapy consisted of leucovorin on day 1, followed by the continuous infusion of 5-FU on days 1 and 2, and oxaliplatin on day 3. In the second and subsequent cycles of chemotherapy, oxaliplatin was administered simultaneously with leucovorin on day 1. (18)F-FLT PET scans were obtained 3 times during the first cycle of chemotherapy: before chemotherapy, 24 h after infusion of 5-FU (day 2), and 48 h after completion of chemotherapy (day 5). The maximum standardized uptake value (SUVMAX) of (18)F-FLT was measured. Treatment responses were assessed by CT after 3 cycles of FOLFOX. **RESULTS:** Eighteen patients were included in the study. The response rate after 3 cycles of FOLFOX was 27.8% (5/18). The SUVMAX was increased in responders ($P = 0.043$) and nonresponders ($P < 0.001$) on day 2 and was decreased, compared with baseline values, on day 5 in responders only ($P = 0.043$). Receiver-operating-characteristic curve analysis indicated that the use of a threshold of an SUVMAX increase on day 2 of $\leq 45.8\%$ resulted in a sensitivity of 100%, specificity of 69.2%, and relative risk of 2.250 ($P = 0.029$) for the diagnosis of responders. Use of a threshold of an SUVMAX decrease on day 5 of $\geq 10.6\%$ resulted in a sensitivity of 100%, specificity of 76.9%, and relative risk of 2.667 ($P = 0.007$). Patients with low (18)F-FLT flare tended to have longer survivals than patients with high flare (2-y overall survival rate, 77.8% vs. 44.4%; $P = 0.051$). **CONCLUSION:** The (18)F-FLT flare observed during 5-FU infusion was associated with poor treatment response in patients with mCRC. The degree of (18)F-FLT flare might be used to predict the outcome of patients who receive infusional 5-FU-based chemotherapy.

[78]

TÍTULO / TITLE: - Repressing DNA Repair to Enhance Chemotherapy: Targeting MyD88 in Colon Cancer.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Jul 3;105(13):926-7. doi: 10.1093/jnci/djt148. Epub 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt148](#)

AUTORES / AUTHORS: - Williamson EA; Hromas R

INSTITUCIÓN / INSTITUTION: - Affiliation of authors: Department of Medicine and the Cancer Center, University of Florida College of Medicine and Shands Health Care System, Gainesville, FL (EAW, RH).

[79]

TÍTULO / TITLE: - Predictive and prognostic factors in second- and third-line erlotinib treatment in NSCLC patients with known status of the EGFR gene.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 19. doi: 10.3892/or.2013.2553.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2553](#)

AUTORES / AUTHORS: - Krawczyk P; Kowalski DM; Wojas Krawczyk K; Szczyrek M; Mlak R; Rolski A; Szudy A; Kieszko R; Winiarczyk K; Milanowski J; Krzakowski M

INSTITUCIÓN / INSTITUTION: - Department of Pneumology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland.

RESUMEN / SUMMARY: - Erlotinib is a reversible tyrosine kinase inhibitor of epidermal growth factor receptor (TKI EGFR). In Poland, as of July 2012, it is used in the treatment only of patients with non-small cell lung cancer (NSCLC) and with EGFR mutation gene after standard chemotherapy failure. The effectiveness of erlotinib in second- or third-line treatment of NSCLC patients without EGFR activating mutation gene remains debatable. Clinical trial results indicated that TKI EGFR showed an efficacy of 70-80% in patients with EGFR mutations, while the clinical response to treatment among unselected Caucasian patients is only 10%. The present study was conducted in a group of 71 patients with inoperable, locally advanced or metastatic NSCLC treated with erlotinib as the second- or third-line therapy. Molecular tests (examination of EGFR mutation and gene amplification) were carried out retrospectively. Objective response rate, overall survival (OS) and progression-free survival (PFS) were calculated. Effects of clinical and molecular factors including the presence of EGFR mutations, EGFR gene amplification, patient performance status, rash, smoking status, time from diagnosis to start of therapy, weight loss and the serum LDH levels were analyzed. An objective response in the form of partial response occurred in only 5 patients (7%), who carried EGFR gene mutation. Median time to PFS for the entire group of patients was 1.5 months and median OS was 10 months. The strongest factors increasing the risk of

progression in patients treated with erlotinib were the absence of activating mutations in the EGFR gene (6fold increased risk) and no treatment-related rash (4.5fold increased risk). The most important factors affecting the risk of early mortality were poor performance status (HR 37.344; P>0.0001), no treatment-related rash (HR 14.9348; P=0.0002) and a short response time on the first-line chemotherapy (HR 9.519; P=0.0445).

[80]

TÍTULO / TITLE: - Serum interferon gamma level predicts recurrence in hepatocellular carcinoma patients after curative treatments.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jun 10. doi: 10.1002/ijc.28311.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28311](#)

AUTORES / AUTHORS: - Lee IC; Huang YH; Chau GY; Huo TI; Su CW; Wu JC; Lin HC

INSTITUCIÓN / INSTITUTION: - Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan; Department of Medicine, National Yang-Ming University Hospital, I-Lan, Taiwan.

RESUMEN / SUMMARY: - Host immunity may have important role in the prognosis of hepatocellular carcinoma (HCC). The aim of this study was to evaluate the correlation between circulating immune regulators and clinical outcome in patients with HCC. Sixty-three HCC patients were prospectively enrolled. Serum levels of interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta), interferon-gamma (IFN-gamma) and interferon gamma-inducible protein 10 (IP-10) were measured, as well as the prevalence of regulatory T cells (Treg), NK+ T cells, invariant natural killer T cells (iNKT), programmed cell death-1 (PD-1)+ CD8+ T cells, T helper 17 cells (Th17), CD69+ and CD45RO+ T cells in peripheral blood mononuclear cells (PBMC). Correlation between these immune regulators and clinical outcome were analyzed. A low serum IFN-gamma level (<50 pg/mL) was significantly associated tumor stage (BCLC stage B: 61.25% vs. stage A: 25%, p = 0.010) and tumor size (>5 cm: 53.8% vs. <5 cm: 25%, p = 0.047). Recurrence-free survival was evaluated in 48 patients receiving curative treatment of HCC. By multivariate analysis, BCLC stage [hazard ratio (HR) = 32.180, p < 0.001], tumor size (HR = 15.373, p = 0.005), AST (HR = 3.796, p = 0.011) and IFN-gamma (HR = 0.354, p = 0.018) levels were independent factors associated with recurrence-free survival. In conclusion, serum IFN-gamma level correlates with tumor stage and tumor size in HCC patients. Patients with lower baseline IFN-gamma levels have a higher risk of tumor recurrence after curative treatment. IFN-gamma may reflect host anti-tumor immunity and may be a potential marker of HCC recurrence after curative treatment.

[81]

TÍTULO / TITLE: - Clofarabine, idarubicin, and cytarabine (CIA) as frontline therapy for patients \leq 60 years with newly diagnosed acute myeloid leukemia (AML).

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

REVISTA / JOURNAL: - Am J Hematol. 2013 Jul 22. doi: 10.1002/ajh.23544.

●● Enlace al texto completo (gratis o de pago) [1002/ajh.23544](#)

AUTORES / AUTHORS: - Nazha A; Kantarjian H; Ravandi F; Huang X; Choi S; Garcia-Manero G; Jabbour E; Borthakur G; Kadia T; Konopleva M; Cortes J; Ferrajoli A; Kornblau S; Daver N; Pemmaraju N; Andreeff M; Estrov Z; Du M; Brandt M; Faderl S

INSTITUCIÓN / INSTITUTION: - Department of Leukemia, The University of Texas - M.D. Anderson Cancer Center, Houston, TX, 77030.

RESUMEN / SUMMARY: - Clofarabine is a second generation nucleoside analogue with activity in adults with acute myeloid leukemia (AML). A phase I trial of clofarabine, idarubicin, and cytarabine (CIA) in relapsed and refractory AML had shown an overall response rate (ORR) of 48%. To explore this combination further, we conducted a phase II study of (CIA) in patients with newly diagnosed AML \leq 60 years. Patients \geq 18-60 years with AML and adequate organ function were enrolled. Induction therapy consisted of clofarabine © 20 mg/m² IV daily (days 1-5), idarubicin (I) 10 mg/m² IV daily (days 1-3), and cytarabine (A) 1 g/m² IV daily (days 1-5). Patients in remission received up to 6 consolidation cycles (C 15 mg/m² x 3, I 8 mg/m² x 2, and A 0.75 g/m² x 3). Fifty-seven patients were evaluable. ORR was 79%. With a median follow up of 10.9 months, the median overall survival (OS) was not reached, the median event-free survival (EFS) was 13.5 months. Most toxicities were \leq grade 2. Four week mortality was 2%. In subgroup analysis, patients \leq 40 years had better OS (P = 0.04) and EFS (P = 0.04) compared to patients > 40 years. Compared to historical patients treated with idarubicin and cytarabine (IA), the OS and EFS were significantly longer for CIA treated patients. In multivariate analysis, CIA retained its favorable impact on OS compared to IA. Thus, CIA is an effective and safe therapy for patients \leq 60 years with newly diagnosed AML.

[82]

TÍTULO / TITLE: - Somatic Mutation Profiling and Associations With Prognosis and Trastuzumab Benefit in Early Breast Cancer.

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

REVISTA / JOURNAL: - J Natl Cancer Inst. 2013 Jul 3;105(13):960-967. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1093/jnci/djt121](#)

AUTORES / AUTHORS: - Loi S; Michiels S; Lambrechts D; Fumagalli D; Claes B; Kellokumpu-Lehtinen PL; Bono P; Kataja V; Piccart MJ; Joensuu H; Sotiriou C

INSTITUCIÓN / INSTITUTION: - Affiliations of authors: Breast Cancer Translational Research Laboratory, Institut Jules Bordet, Universite Libre de Bruxelles, Brussels, Belgium (SL, SM, DF, CS); Department of Biostatistics and Epidemiology, Institut Gustave Roussy, Villejuif, France (SM); Vesalius Research Centre, KU Leuven and VIB, Leuven, Belgium (DL, BC); Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium (DL, BC); Department of Oncology, Tampere University Hospital, Tampere, Finland (P-LK-L); Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland (PB, HJ); Cancer Center, Kuopio University Hospital, Kuopio, Finland (VK); Department of Medicine, Institut Jules Bordet, Brussels, Belgium (MJP).

RESUMEN / SUMMARY: - **BACKGROUND:** Certain somatic alterations in breast cancer can define prognosis and response to therapy. This study investigated the frequencies, prognostic effects, and predictive effects of known cancer somatic mutations using a randomized, adjuvant, phase III clinical trial dataset. **METHODS:** The FinHER trial was a phase III, randomized adjuvant breast cancer trial involving 1010 women. Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer were further randomized to 9 weeks of trastuzumab or no trastuzumab. Seven hundred five of 1010 tumors had sufficient DNA for genotyping of 70 somatic hotspot mutations in 20 genes using mass spectrometry. Distant disease-free survival (DDFS), overall survival (OS), and interactions with trastuzumab were explored with Kaplan-Meier and Cox regression analyses. All statistical tests were two-sided. **RESULTS:** Median follow-up was 62 months. Of 705 tumors, 687 were successfully genotyped. PIK3CA mutations (exons 1, 2, 4, 9, 13, 18, and 20) were present in 25.3% (174 of 687) and TP53 mutations in 10.2% (70 of 687). Few other mutations were found: three ERBB2 and single cases of KRAS, ALK, STK11/LKB1, and AKT2. PIK3CA mutations were associated with estrogen receptor positivity ($P < .001$) and the luminal-A phenotype ($P = .04$) but were not statistically significantly associated with prognosis (DDFS: hazard ratio [HR] = 0.88, 95% confidence [CI] = 0.58 to 1.34, $P = .56$; OS: HR = 0.603, 95% CI = .32 to 1.13, $P = .11$), although a statistically significant nonproportional prognostic effect was observed for DDFS ($P = .002$). PIK3CA mutations were not statistically significantly associated with trastuzumab benefit (P interaction: DDFS $P = .14$; OS $P = .24$). **CONCLUSIONS:** In this dataset, targeted genotyping revealed only two alterations at a frequency greater than 10%, with other mutations observed infrequently. PIK3CA mutations were associated with a better outcome, however this effect disappeared after 3 years. There were no statistically significant associations with trastuzumab benefit.

TÍTULO / TITLE: - Prognostic significance of immunohistochemical expression of the angiogenic molecules vascular endothelial growth factor-A, vascular endothelial growth factor receptor-1 and vascular endothelial growth factor receptor-2 in patients with classical Hodgkin lymphoma.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 16.

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

[3109/10428194.2013.813629](#)

AUTORES / AUTHORS: - Dimtsas GS; Georgiadi EC; Karakitsos P; Vassilakopoulos TP; Thymara I; Korkolopoulou P; Patsouris E; Kittas C; Doussis-Anagnostopoulou IA

INSTITUCIÓN / INSTITUTION: - Department of Histology and Embryology.

RESUMEN / SUMMARY: - Angiogenesis leads to new blood vessel formation and is implicated in both physiological and pathological situations. The vascular endothelial growth factor (VEGF) family is the major mediator of this process. The aim of our study was to evaluate the expression of VEGF-A, vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGFR-2 and their correlation with clinicopathological parameters and prognosis in patients with classical Hodgkin lymphoma (cHL), since the role of angiogenesis in this tumor still remains unclear. The immunohistochemical expression of VEGF-A, VEGFR-1 and VEGFR-2 was examined in 194 patients with cHL. The neoplastic Hodgkin Reed-Sternberg (HRS) cells expressed VEGF-A, VEGFR-1 and VEGFR-2 in 90.3%, 97.2% and 94.1% of cases, respectively. Only the expression of VEGFR-2 was positively correlated with serum albumin levels ≥ 4 g/dL. No correlation with patient outcome was observed. All three molecules were statistically correlated with ramifications of blood vessels. Summarizing, our results are not sufficient to consider VEGF-A and/or VEGF receptors as prognosticators in cHL.

[84]

TÍTULO / TITLE: - A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jun 27. pii: S0959-8049(13)00428-0. doi: 10.1016/j.ejca.2013.05.020.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.05.020](#)

AUTORES / AUTHORS: - Liu JF; Tolaney SM; Birrer M; Fleming GF; Buss MK; Dahlberg SE; Lee H; Whalen C; Tyburski K; Winer E; Ivy P; Matulonis UA

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States. Electronic address:

joyce_liu@dfci.harvard.edu.

RESUMEN / SUMMARY: - BACKGROUND: Poly(ADP-ribose) polymerase (PARP)-inhibitors and anti-angiogenics have activity in recurrent ovarian and breast cancer; however, the effect of combined therapy against PARP and angiogenesis in this population has not been reported. We investigated the toxicities and recommended phase 2 dosing (RP2D) of the combination of cediranib, a multitargeted inhibitor of vascular endothelial growth factor receptor (VEGFR)-1/2/3 and olaparib, a PARP-inhibitor (NCT01116648). METHODS: Cediranib tablets once daily and olaparib capsules twice daily were administered orally in a standard 3+3 dose escalation design. Patients with recurrent ovarian or metastatic triple-negative breast cancer were eligible. Patients had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or met Gynecologic Cancer InterGroup (GCIg) CA125 criteria. No prior PARP-inhibitors or anti-angiogenics in the recurrent setting were allowed. RESULTS: 28 patients (20 ovarian, 8 breast) enrolled to 4 dose levels. 2 dose limiting toxicities (DLTs) (1 grade 4 neutropenia 4days; 1 grade 4 thrombocytopenia) occurred at the highest dose level (cediranib 30mg daily; olaparib 400mg twice daily [BID]). The RP2D was cediranib 30mg daily and olaparib 200mg BID. Grade 3 or higher toxicities occurred in 75% of patients, and included grade 3 hypertension (25%) and grade 3 fatigue (18%). One grade 3 bowel obstruction occurred. The overall response rate (ORR) in the 18 RECIST-evaluable ovarian cancer patients was 44%, with a clinical benefit rate (ORR plus stable disease (SD) >24weeks) of 61%. None of the seven evaluable breast cancer patients achieved clinical response; two patients had stable disease for >24weeks. INTERPRETATION: The combination of cediranib and olaparib has haematologic DLTs and anticipated class toxicities, with promising evidence of activity in ovarian cancer patients.

[85]

TÍTULO / TITLE: - Hepatic activation of irinotecan predicts tumour response in patients with colorectal liver metastases treated with DEBIRI: exploratory findings from a phase II study.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug;72(2):359-68. doi: 10.1007/s00280-013-2199-5. Epub 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2199-](#)

[5](#)

AUTORES / AUTHORS: - Jones RP; Sutton P; Greensmith RM; Santoyo-Castelazo A; Carr DF; Jenkins R; Rowe C; Hamlett J; Park BK; Terlizzo M; O'Grady E; Ghaneh P; Fenwick SW; Malik HZ; Poston GJ; Kitteringham NR

INSTITUCIÓN / INSTITUTION: - School of Cancer Studies, Institute of Translational Medicine, University of Liverpool, Liverpool, L69 3GA, UK, robjones@liv.ac.uk.

RESUMEN / SUMMARY: - PURPOSE: The response of colorectal liver metastases to the cytotoxic agent irinotecan varies widely. Attempts to correlate tumour

metabolism with response have been mixed. This study investigated the hepatic metabolism of irinotecan as a potential predictor of tumour response to irinotecan-eluting beads (DEBIRI). METHODS: Ten patients with colorectal liver metastases were treated with 200 mg irinotecan (as DEBIRI) as part of the PARAGON II study. Hepatic expression of key metabolising enzymes was measured using mass spectrometry-based proteomics. Serum drug concentrations and hepatic irinotecan metabolism were characterised and correlated with tumour response. RESULTS: Serum concentrations of irinotecan metabolites did not correlate with hepatic metabolism or pathological response. There was a strong correlation between hepatic CES-2 expression and activation of irinotecan ($r(2) = 0.96, p < 0.001$). Patients with a UGT1A1*28 6/7 SNP showed no difference in drug metabolism or pathological response. Hepatic CES-2 mediated activation of irinotecan clearly correlated with tumour replacement by fibrosis ($r(2) = 0.54, p = 0.01$). CONCLUSION: This study provides the first evidence that hepatic activation of irinotecan predicts tumour response. Delivery of liver-targeted irinotecan to normal liver tissue rather than tumour may be a more rational approach to maximise response.

[86]

TÍTULO / TITLE: - Involvement of MAPK activation and ROS generation in human leukemia U937 cells undergoing apoptosis in response to sonodynamic therapy.

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

REVISTA / JOURNAL: - Int J Radiat Biol. 2013 Jul 8.

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

[3109/09553002.2013.817700](#)

AUTORES / AUTHORS: - Su X; Wang P; Wang X; Guo L; Li S; Liu Q

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Medicinal Resources and Natural Pharmaceutical Chemistry, Ministry of Education, National Engineering Laboratory for Resource Developing of Endangered Chinese Crude Drugs in Northwest of China, College of Life Sciences, Shaanxi Normal University, Xi'an, P. R. China.

RESUMEN / SUMMARY: - Purpose: To elucidate the underlying events in Chlorin e6 (Ce6)-mediated sonodynamic therapy (SDT) (Ce6-SDT)-induced apoptosis of human leukemia cell line U937. Materials and methods: The viability of cells was determined by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltertrazolium bromide tetrazolium (MTT) test. Apoptosis was analyzed using a flow cytometer as well as fluorescence microscopy with 4'-6-Diamidino-2-Phenylindole (DAPI) staining. Western blotting was used to analyze the expression of caspase-3, poly ADP-ribose polymerase (PARP) and mitogen-activated protein kinase (MAPK). Results: Several distinct sonochemical effects were found after SDT treatment. The participation of MAPK signals in SDT which caused U937 cell damage was specifically examined and the inhibition of p38 MAPK and Jun-N-terminal kinase (JNK) both apparently exerted a

negative effect on SDT-induced cell death, while extracellular signal-regulating kinase (ERK1/2) inhibition enhanced SDT-induced cell death. The intracellular reactive oxygen species (ROS) was significantly enhanced by SDT, and pre-treatment with ROS scavenger N-acetylcysteine (NAC) partially alleviated SDT-induced cell viability loss, DNA fragmentation, mitochondria membrane potential (MMP) dissipation, caspase-3 activation, but interestingly MAPK activation was not affected much by NAC. Conclusions: In the present paper, cell apoptosis of U937 cells was markedly enhanced after Ce6-SDT. Meanwhile, p38 MAPK, JNK and ERK were all differently activated in this process. One possible explanation for the induced cell apoptosis could be the increased ROS generation in Ce6-SDT.

[87]

TÍTULO / TITLE: - Reactivation of hepatitis B virus in a hepatitis B surface antigen-negative patient with acute promyelocytic leukemia treated with arsenic trioxide.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jun 1.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1804-](#)

[3](#)

AUTORES / AUTHORS: - Yujiri T; Tanaka M; Taguchi A; Tanaka Y; Nakamura Y; Tanizawa Y

INSTITUCIÓN / INSTITUTION: - Third Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Yamaguchi, 755-8505, Japan, yujirit@yamaguchi-u.ac.jp.

[88]

TÍTULO / TITLE: - RECIST 1.1 in NSCLC Patients With EGFR Mutations Treated With EGFR Tyrosine Kinase Inhibitors: Comparison With RECIST 1.0.

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

REVISTA / JOURNAL: - AJR Am J Roentgenol. 2013 Jul;201(1):W64-71. doi: 10.2214/AJR.12.9668.

●● Enlace al texto completo (gratis o de pago) [2214/AJR.12.9668](#)

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

INSTITUCIÓN / INSTITUTION: - 1 Department of Imaging Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave., Boston MA 02215.

RESUMEN / SUMMARY: - OBJECTIVE. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 has been rapidly accepted in clinical trials as a standard measure to assess tumor response to therapy and is expected to improve response assessment, especially in genomically defined patients. The impact of RECIST 1.1 was compared with RECIST 1.0 in non-small cell lung cancer

(NSCLC) patients with sensitizing epidermal growth factor receptor (EGFR) mutations treated with EGFR tyrosine kinase inhibitors. MATERIALS AND METHODS. Seventy patients with advanced NSCLC harboring sensitizing EGFR mutations treated with a first-line EGFR tyrosine kinase inhibitor were retrospectively studied. Tumor measurements and response assessment were performed using RECIST 1.0 and RECIST 1.1. The number of target lesions, the percentage change at the initial follow-up, best response, and time to progression were compared between RECIST 1.1 and RECIST 1.0. RESULTS. The number of target lesions identified using RECIST 1.1 was significantly lower compared with that using RECIST 1.0 (mean, 2.7 and 2.0, respectively; $p < 0.0001$; paired Student t test), with a decrease in 31 patients (44%). The initial proportional changes of the target lesion measurements had high correlation between the two criteria ($R(2) = 0.8070$), with concordant response assessment in 66 patients (94%). The best response showed almost perfect agreement ($kappa = 0.970$). Time to progression (TTP) did not differ between the two criteria in 52 patients (74%), was longer by RECIST 1.1 in 15 patients (21%), and was shorter by RECIST 1.1 in three patients (4%). CONCLUSION. RECIST 1.1 provided highly concordant response assessment with a decreased number of target lesions compared with RECIST 1.0 in advanced NSCLC patients harboring sensitizing EGFR mutations treated with an EGFR tyrosine kinase inhibitor. RECIST 1.1 altered TTP in 25% of patients compared with RECIST 1.0.

[89]

TÍTULO / TITLE: - Solitary Brain Metastasis As First Manifestation of Small-Cell Parotid Gland Carcinoma With High Sensitivity to Temozolomide Therapy on Basis of Tumor O6-Methylguanine-DNA-Methyltransferase Expression.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 10;31(23):e394-7. doi: 10.1200/JCO.2012.47.5590. Epub 2013 Jun 24.

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

[1200/JCO.2012.47.5590](#)

AUTORES / AUTHORS: - Lolli I; Morra I; Cimmino A; Trevisan E; Ruda R; Piombino M; Campanella G; Gillio Tos A; De Marco L; Trevisan M; Fiano V; Soffiatti R

INSTITUCIÓN / INSTITUTION: - Medical Oncology, Istituto Di Ricovero e Cura a Carattere Scientifico Saverio de Bellis, 70013 via Turi, 27 Castellana Grotte (Bari), Italy; ivanlolli1@tin.it.

[90]

TÍTULO / TITLE: - Requirement for anti-apoptotic MCL-1 in the survival of BCR-ABL B-lineage acute lymphoblastic leukemia.

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

REVISTA / JOURNAL: - Blood. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2012-06-440230](#)

AUTORES / AUTHORS: - Koss B; Morrison J; Perciavalle RM; Singh H; Rehg JE; Williams RT; Opferman JT

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, TN, United States;

RESUMEN / SUMMARY: - The response of Philadelphia chromosome (Ph+) acute lymphoblastic leukemia (ALL) to treatment by BCR-ABL tyrosine kinase inhibitors (TKIs) has been disappointing, often resulting in short remissions typified by rapid outgrowth of drug-resistant clones. Therefore, new treatments are needed to improve outcomes for Ph+ ALL patients. In a mouse model of Ph+ B-lineage ALL (B-ALL), MCL-1 expression is dysregulated by the BCR-ABL oncofusion protein and TKI treatment results in loss of MCL-1 expression prior to the induction of apoptosis, suggesting that MCL-1 may be an essential pro-survival molecule. To test this hypothesis, we developed a mouse model in which conditional allele(s) of Mcl-1 can be deleted either during leukemia transformation or later after the establishment of leukemia. We report that endogenous MCL-1's anti-apoptotic activity promotes survival during BCR-ABL transformation and in established BCR-ABL+ leukemia. This requirement for MCL-1 can be overcome by overexpression of other anti-apoptotic molecules. We further demonstrate that strategies to inhibit MCL-1 expression potentiate the pro-apoptotic action of BCL-2 inhibitors in both mouse and human BCR-ABL+ leukemia cell lines. Thus, strategies focused on antagonizing MCL-1 function and expression would be predicted to be effective therapeutic strategies.

[91]

TÍTULO / TITLE: - HER3 status by immunohistochemistry is correlated with poor prognosis in hormone receptor-negative breast cancer patients.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jun;139(3):741-50. doi: 10.1007/s10549-013-2570-6. Epub 2013 May 31.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2570-6](#)

AUTORES / AUTHORS: - Bae SY; La Choi Y; Kim S; Kim M; Kim J; Jung SP; Choi MY; Lee SK; Kil WH; Lee JE; Nam SJ

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea.

RESUMEN / SUMMARY: - Breast cancer is a highly heterogeneous malignancy. The triple-negative breast cancer (TNBC) and human epidermal growth factor

receptor 2 (HER2) breast cancer subtypes are highly aggressive and are associated with a poor prognosis. The therapeutic targets for TNBC remain undefined, and many patients with the HER2 subtype acquire resistance to therapy after prolonged treatment. The objective of this study was to evaluate the prognostic significance of HER3 expression in invasive breast carcinoma. We established matched tissue microarray (TMA) blocks and clinical data from 950 cases of invasive breast carcinoma with long-term clinical follow-up data (median 109.7 months). Using the TMAs, we characterized the expression of ER, PR, HER2, EGFR, and HER3 by immunohistochemistry. Each case was classified as one of four IHC-based subtypes based on the expression of hormonal receptor (HR) and HER2. The clinicopathological characteristics and survival of 950 patients were analyzed by subtype. In the TNBC subtype, the HER3(+) group showed poorer disease-free survival (DFS, $P = 0.010$) and overall survival (OS, $P = 0.015$) than the HER3(-) group. In the HER2 subtype, the HER3(+) group also showed poorer DFS ($P = 0.022$) and OS ($P = 0.077$) than the HER3(-) group. However, there was no difference in patients with HR-positive breast cancer. HER3 expression was associated with poor DFS in both the TNBC and HER2 subtypes and poor OS in the TNBC subtype. HER3 overexpression is an important prognostic marker in hormone receptor-negative breast cancer, and further study is needed to clarify the role of HER-3 targeted treatment.

[92]

TÍTULO / TITLE: - Long-term results of the Polish Adult Leukemia Group PALG-CLL2 phase III randomized study comparing cladribine-based combinations in chronic lymphocytic leukemia.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 May 31.

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

[3109/10428194.2013.809073](#)

AUTORES / AUTHORS: - Robak T; Blonski JZ; Gora-Tybor J; Calbecka M; Dwilewicz-Trojaczek J; Boguradzki P; Dmoszynska A; Kowal M; Kloczko J; Piszcz J; Stella-Holowiecka B; Sulek K; Kuliczowski K; Potoczek S; Warzocha K; Lech-Maranda E; Skotnicki AB; Piotrowska M; Moskwa A; Zawilska K; Jamroziak K

RESUMEN / SUMMARY: - Abstract Long-term outcomes following newer therapies for chronic lymphocytic leukemia (CLL) have rarely been reported. This paper presents the results of the final analysis of the Polish Adult Leukemia Group PALG-CLL2 study performed ten years from final patient enrollment. With the extended follow-up time, it was found that cladribine (2-CdA)-based combinations, CMC (2-CdA, cyclophosphamide, mitoxantrone) and CC (2-CdA, cyclophosphamide) administered as first-line treatment of progressive CLL result in significantly longer progression-free survival, but similar overall survival

compared to 2-CdA monotherapy. Furthermore, the risk of potentially fatal late adverse events including infections, autoimmune complications and, particularly, secondary neoplasms is comparable among patients treated with CMC, CC or 2-CdA. The results of our analysis support the importance of long-term outcome monitoring of randomized trials in CLL.

[93]

TÍTULO / TITLE: - Testing personalized medicine: patient and physician expectations of next-generation genomic sequencing in late-stage cancer care.

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

REVISTA / JOURNAL: - Eur J Hum Genet. 2013 Jul 17. doi: 10.1038/ejhg.2013.158.

●● Enlace al texto completo (gratis o de pago) [1038/ejhg.2013.158](#)

AUTORES / AUTHORS: - Miller FA; Hayeems RZ; Bytautas JP; Bedard PL; Ernst S; Hirte H; Hotte S; Oza A; Razak A; Welch S; Winquist E; Dancey J; Siu LL

INSTITUCIÓN / INSTITUTION: - 1] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada [2] Joint Centre for Bioethics, University of Toronto, Toronto, ON, Canada.

RESUMEN / SUMMARY: - Developments in genomics, including next-generation sequencing technologies, are expected to enable a more personalized approach to clinical care, with improved risk stratification and treatment selection. In oncology, personalized medicine is particularly advanced and increasingly used to identify oncogenic variants in tumor tissue that predict responsiveness to specific drugs. Yet, the translational research needed to validate these technologies will be conducted in patients with late-stage cancer and is expected to produce results of variable clinical significance and incidentally identify genetic risks. To explore the experiential context in which much of personalized cancer care will be developed and evaluated, we conducted a qualitative interview study alongside a pilot feasibility study of targeted DNA sequencing of metastatic tumor biopsies in adult patients with advanced solid malignancies. We recruited 29/73 patients and 14/17 physicians; transcripts from semi-structured interviews were analyzed for thematic patterns using an interpretive descriptive approach. Patient hopes of benefit from research participation were enhanced by the promise of novel and targeted treatment but challenged by non-findings or by limited access to relevant trials. Family obligations informed a willingness to receive genetic information, which was perceived as burdensome given disease stage or as inconsequential given faced challenges. Physicians were optimistic about long-term potential but conservative about immediate benefits and mindful of elevated patient expectations; consent and counseling processes were expected to mitigate challenges from incidental findings. These findings suggest the need for information and decision tools to support physicians in communicating realistic prospects of benefit, and for cautious approaches to the

generation of incidental genetic information. European Journal of Human Genetics advance online publication, 17 July 2013; doi:10.1038/ejhg.2013.158.

[94]

TÍTULO / TITLE: - Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population.

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

REVISTA / JOURNAL: - J Urol. 2013 Jun 11. pii: S0022-5347(13)04603-X. doi: 10.1016/j.juro.2013.06.017.

●● Enlace al texto completo (gratis o de pago) 1016/j.juro.2013.06.017

AUTORES / AUTHORS: - Karnes RJ; Bergstralh EJ; Davicioni E; Ghadessi M; Buerki C; Mitra AP; Crisan A; Erho N; Vergara IA; Lam LL; Carlson R; Thompson DJ; Haddad Z; Zimmermann B; Sierocinski T; Triche TJ; Kollmeyer T; Ballman KV; Black PC; Klee GG; Jenkins RB

INSTITUCIÓN / INSTITUTION: - Department of Urology, Mayo Clinic, Rochester, MN, USA. Electronic address: karnes.r@mayo.edu.

RESUMEN / SUMMARY: - **PURPOSE:** Prostate cancer patients with locally advanced disease after radical prostatectomy (RP) are candidates for secondary therapy. However, this higher risk population is heterogeneous and many will not metastasize even when conservatively managed. Given the limited specificity of pathologic features to predict metastasis, newer risk-prediction models are needed. This represents a validation study of a genomic classifier (GC) that predicts post-RP metastasis in a high-risk population. **MATERIALS AND METHODS:** A case-cohort design was used to sample 1,010 post-RP patients at high risk of recurrence treated between 2000-2006. Patients had preoperative PSA >20 ng/mL, Gleason \geq 8, pT3b or GPSM score \geq 10. Patients with metastasis at diagnosis or any prior treatment for prostate cancer were excluded. 20% random sampling created a subcohort that included all cases with metastasis. 22-marker GC scores were generated for 219 patients with available genomic data. Receiver operating characteristic and decision curves, competing risk, and weighted regression models assessed GC performance. **RESULTS:** GC had area under the curve of 0.79 for predicting 5-year metastasis post-RP. Decision curves showed that net benefit of GC exceeded clinical-only models. GC was the predominant predictor of metastasis in multivariable analysis. Cumulative incidence of metastasis at 5 years post-RP was 2.4%, 6.0% and 22.5% for patients with low (60% of patients), intermediate (21% of patients), and high (19% of patients) GC scores, respectively ($p < 0.001$). **CONCLUSIONS:** These results indicate that genomic information from the primary tumor can identify patients with adverse pathology who are most at risk for metastasis and potentially lethal prostate cancer.

[95]

TÍTULO / TITLE: - Value of the pretreatment albumin to globulin ratio in predicting long-term mortality in breast cancer patients.

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

REVISTA / JOURNAL: - Am J Surg. 2013 Jul 15. pii: S0002-9610(13)00316-4. doi: 10.1016/j.amjsurg.2013.03.007.

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

[1016/j.amjsurg.2013.03.007](#)

AUTORES / AUTHORS: - Azab BN; Bhatt VR; Vonfrolio S; Bachir R; Rubinshteyn V; Alkaied H; Habeshy A; Patel J; Picon AI; Bloom SW

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, USA. Electronic address: basemnady2000@yahoo.com.

RESUMEN / SUMMARY: - BACKGROUND: Prior studies have demonstrated the prognostic value of pretreatment serum albumin in different types of cancer. The aim of this study was to assess the predictive value of the albumin to globulin ratio (AGR) on survival in breast cancer patients. METHODS: This retrospective study used an unselected cohort of 354 breast cancer patients who had documented total protein and albumin levels prior to chemotherapy. Survival status was obtained from our cancer registry. Survival analysis, stratified by AGR tertiles, was used to evaluate the prognostic value of AGR. RESULTS: Patients in the highest AGR tertiles (AGR > 1.45) had a lower 5-year mortality rate compared with those in the middle (AGR 1.21 to 1.45) and the lowest (AGR < 1.21) tertiles (6% vs 18% and 32%, P < .001). After adjusting for confounding variables, AGR remained a significant predictor of mortality (P < .002). Moreover, after excluding the patients with albumin levels less than 3.6, the AGR remained a significant predictor of survival (P .0018). CONCLUSIONS: Pretreatment AGR is an independent, significant predictor of long-term mortality in breast cancer patients, even in patients with normal albumin levels.

[96]

TÍTULO / TITLE: - Analysis of UGT1A1*28 genotype and SN-38 pharmacokinetics for irinotecan-based chemotherapy in patients with advanced colorectal cancer: results from a multicenter, retrospective study in Shanghai.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1480-](#)

[7](#)

AUTORES / AUTHORS: - Cai X; Cao W; Ding H; Liu T; Zhou X; Wang M; Zhong M; Zhao Z; Xu Q; Wang L

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Shanghai First People's Hospital, Shanghai Jiaotong University, 100 Haining Road, Hongkou District, Shanghai, 200080, People's Republic of China, caixuncn@163.com.

RESUMEN / SUMMARY: - BACKGROUND: The UGT1A1*28 polymorphism, although closely linked with CPT-11-related adverse effects, cannot be used alone to guide individualized treatment decisions. However, CPT-11 dosage can be adjusted according to measured SN-38 pharmacokinetics. Our study is designed to investigate whether there is a relationship between SN-38 peak or valley concentrations and efficacy or adverse effects of CPT-11-based chemotherapy. We retrospectively studied 98 patients treated with advanced colorectal cancer in various UGT1A1*28 genotype groups (mainly (TA)6/(TA)6 and (TA)6/(TA)7 genotypes) treated with CPT-11 as first-line chemotherapy in Shanghai. METHODS: One hundred and sixty-four advanced colorectal cancer patients were enrolled. To understand differences in genotype expression, the frequency of UGT1A1*28 thymine-adenine (TA) repeats in TATA box arrangement was assessed by PCR with genomic DNA extracted from peripheral blood. For ninety-eight cases with the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes treated with CPT-11 as first-line chemotherapy, the plasma concentration of SN-38 was detected by HPLC 1.5 and 49 h after CPT-11 infusion. Efficacy and adverse effects were observed subsequently, and the relationship between SN-38 plasma concentration and efficacy or adverse effects within genotype groups, as well as differences in efficacy and adverse effects between (TA)6/(TA)6 and (TA)6/(TA)7 genotypes were analyzed statistically. RESULTS: One hundred and fourteen patients (69.51 %) were identified with the (TA)6/(TA)6 genotype, forty-eight patients (29.27 %) with the (TA)6/(TA)7 genotype, and two patients (1.22 %) with the (TA)7/(TA)7 genotype. The average peak and valley concentrations of SN-38 after CPT-11 infusion and plasma bilirubin average levels before and after CPT-11 treatment in the (TA)6/(TA)7 genotype group were all higher than those in (TA)6/(TA)6 group, and the difference was statistically significant ($p = 0.00$). Stepwise regression analysis showed that SN-38 peak and valley concentration was correlated with PFS in the (TA)6/(TA)6 genotype. In the (TA)6/(TA)7 group, SN-38 peak concentration was correlated with CPT-11 starting dose and OS, valley concentration correlated with plasma bilirubin levels before CPT-11 treatment, delayed diarrhea, and OS. For the (TA)6/(TA)6 genotype, mPFS of the SN-38 peak concentration >43.2 ng/ml subgroup was significantly longer than that of ≤ 43.2 ng/ml subgroup (8.0 ± 0.35 vs. 6.5 ± 0.79 months, $\chi^2 = 17.18$, $p = 0.00$) with a relatively high incidence of Grade I/II degrees myelosuppression; for the (TA)6/(TA)7 genotype, there was no significant difference in mOS between the SN-38 valley concentration >16.83 ng/ml and ≤ 16.83 subgroups (17.3 ± 0.45 vs. 18.8 ± 0.50 months, $\chi^2 = 1.38$, $p = 0.24$), but the former had a higher incidence of Grade III/IV degrees mucositis and delayed diarrhea. For 2 (TA)7/(TA)7 cases, although 25 % dose reduction of CPT-11, which is calculated according to body surface area, Grade IV degrees bone marrow suppression and Grade III degrees delayed diarrhea still occurred after CPT-11 treatment, though both adverse effects resolved and did not recur again after a 50 % dose reduction. CONCLUSION: The (TA)6/(TA)6 genotype and

(TA)6/(TA)7 genotype accounted for the most, and (TA)7/(TA)7 genotype only account for a very small portion of advanced colorectal cancer patients in Shanghai. For the (TA)6/(TA)6 genotype, CPT-11 dosage can be increased gradually to improve efficacy for patients with SN-38 peak concentration ≤ 43.2 ng/ml after CPT-11 infusion; and for (TA)6/(TA)7 genotype patients, CPT-11 dosage may be lowered appropriately to reduce serious adverse effects such as bone marrow suppression and delayed diarrhea without affecting the efficacy for those with SN-38 valley concentration > 16.83 ng/ml. For (TA)7/(TA)7 genotype patients, adverse effects should be closely observed after treatment even if CPT-11 dosage has been reduced.

[97]

TÍTULO / TITLE: - Effect of bone marrow mesenchymal stem cells from blastic phase chronic myelogenous leukemia on the growth and apoptosis of leukemia cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Aug;30(2):1007-13. doi: 10.3892/or.2013.2518. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2518](#)

AUTORES / AUTHORS: - Han Y; Wang Y; Xu Z; Li J; Yang J; Li Y; Shang Y; Luo J

INSTITUCIÓN / INSTITUTION: - Department of Hematology, The Second Hospital, Hebei Medical University, Shijiazhuang, Hebei 050000, P.R. China.

RESUMEN / SUMMARY: - Chronic myelogenous leukemia (CML) has a typical progressive course with transition from a chronic phase to a terminal blast crisis phase. However, the mechanisms that lead to disease progression remain unclear. Bone marrow mesenchymal stem cells (BMMSCs) play important roles in maintaining the bone marrow microenvironment. In the present study, the biological characteristics of BMMSCs were determined including proliferation, apoptosis and secretion of cytokines during blastic phase CML (CML-Bp). The effect of BMMSCs in CML-Bp on K562 human CML cells and the CML-Bp original generation leukemia cells were also explored. Our results showed that CML-Bp BMMSCs protect tumor cells and increase their anti-apoptotic ability through regulating the expression of apoptosis-related proteins and activating the Wnt pathway.

[98]

TÍTULO / TITLE: - Factors predicting temozolomide induced clinically significant acute hematologic toxicity in patients with high-grade gliomas: A clinical audit.

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

REVISTA / JOURNAL: - Clin Neurol Neurosurg. 2013 Jun 10. pii: S0303-8467(13)00171-6. doi: 10.1016/j.clineuro.2013.05.015.

- Enlace al texto completo (gratis o de pago)

[1016/j.clineuro.2013.05.015](#)

AUTORES / AUTHORS: - Gupta T; Mohanty S; Moiyadi A; Jalali R

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Advanced Centre for Treatment Research & Education in Cancer (ACTREC) and Tata Memorial Hospital (TMH) Tata Memorial Centre, Mumbai, India. Electronic address: tejpalgupta@rediffmail.com.

RESUMEN / SUMMARY: - INTRODUCTION: Myelo-suppression, the dose-limiting toxicity of alkylating cytotoxic agents is generally perceived to be uncommon with temozolomide (TMZ), a novel oral second generation imidazotetrazinone prodrug, with a reported incidence of 5-10% of grade 3-4 acute hematologic toxicity. We were observing a higher incidence of clinically significant myelo-toxicity with the standard schedule of TMZ, particularly in females, prompting us to do a clinical audit in our patient population. METHODS: One hundred two adults (>18 years of age) treated with TMZ either for newly diagnosed or recurrent/progressive high-grade glioma constituted the study cohort. Clinically significant acute hematologic toxicity was defined as any one or more of the following: any grade 3-4 hematologic toxicity; omission of daily TMZ dose for ≥ 3 consecutive days during concurrent phase; deferral of subsequently due TMZ cycle by ≥ 7 days during adjuvant phase; dose reduction or permanent discontinuation of TMZ; use of growth factors, platelets or packed-cell transfusions during the course of TMZ. Uni-variate and multi-variate analysis was performed to correlate incidence of acute hematologic toxicity with baseline patient, disease, and treatment characteristics. RESULTS: The incidence of clinically significant neutropenia and thrombocytopenia was 7% and 12% respectively. Seven (7%) patients needed packed-cells, growth factors, and/or platelet transfusions. Grade 3-4 lymphopenia though common (32%) was self-limiting and largely asymptomatic. Two (2%) patients, both women succumbed to community acquired pneumonia during adjuvant TMZ. Multi-variate logistic regression analysis identified female gender, grade IV histology, baseline total leukocyte count $< 7700/\text{mm}^3$ and baseline serum creatinine $\geq 1\text{mg/dl}$ as factors associated with significantly increased risk of clinically significant acute hematologic toxicity. CONCLUSION: The incidence of TMZ induced clinically significant neutropenia and thrombocytopenia was low in our patient population. Severe lymphopenia though high was largely asymptomatic and self-limiting. Gender, grade, leukocyte count, and serum creatinine were significant independent predictors of severe acute myelo-toxicity.

[99]

TÍTULO / TITLE: - Sequential use of protein kinase inhibitors potentiates their toxicity to melanoma cells: A rationale to combine targeted drugs based on protein expression inhibition profiles.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Sep;43(3):919-26. doi: 10.3892/ijo.2013.2008. Epub 2013 Jul 8.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2008](https://doi.org/10.3892/ijo.2013.2008)

AUTORES / AUTHORS: - Aftimos PG; Wiedig M; Langouo Fontsa M; Awada A; Ghanem G; Journe F

INSTITUCIÓN / INSTITUTION: - Medical Oncology Clinic, Free University of Brussels, 1000 Brussels, Belgium.

RESUMEN / SUMMARY: - Targeted therapy has shown high efficacy in the treatment of metastatic melanoma with impressive response rates. However, resistance appears after a few months, underlining the need for simultaneous multiple signalling pathway inhibition to provide a durable benefit. The aim of our study was to evaluate the possible synergistic effect of various protein kinase inhibitor combinations targeting SRC, MEK, PI3K or JAK on the survival of representative melanoma cell lines with WTNRAS/WTBRAF and harbouring the most frequent mutations (Q61LNRAS/WTBRAF or WTNRAS/V600EBRAF). By comparing IC50s and protein inhibition profiles, cell exposure to a single inhibitor for 3 days (condition 1) showed that both WTBRAF lines were at least 15-fold more sensitive to SRC inhibition while V600EBRAF cells were 30-fold more sensitive to MEK inhibition, confirming that the latter cells are largely dependent on the MAPK pathway for growth. Concomitant treatment for 3 days (condition 2) revealed an antagonistic effect between SRC and JAK inhibitors as compared to treatment by each inhibitor alone in all 3 lines, supporting that both SRC and JAK stimulate the STAT pathway. Finally, sequential cell exposure to inhibitors by pre-treatment with a single effector at non-toxic but effective on target inhibition concentrations for 7 days followed by the addition of each of the other inhibitors for 3 days (condition 3) showed that MEK, PI3K or JAK inhibitor acted in synergy with the SRC inhibitor in both wild-type and Q61LNRAS cells, suggesting that the first inhibitor could activate the SRC/STAT compensatory signalling pathway. In conclusion, a treatment strategy consisting in a sequential use of targeted inhibitors to first render melanoma cells more dependent on alternative compensatory pathways that should subsequently be inhibited, may enhance efficacy. By contrast, concomitant exposure to various combinations of inhibitors at different concentrations failed to produce such effect, further supporting the importance of both the duration of cell exposure to inhibitors and their sequential use.

[100]

TÍTULO / TITLE: - Circulating nucleosomes and immunogenic cell death markers HMGB1, sRAGE and DNase in patients with advanced pancreatic cancer undergoing chemotherapy.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jun 1. doi: 10.1002/ijc.28294.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28294](https://doi.org/10.1002/ijc.28294)

AUTORES / AUTHORS: - Wittwer C; Boeck S; Heinemann V; Haas M; Stieber P; Nagel D; Holdenrieder S

INSTITUCIÓN / INSTITUTION: - Institute of Clinical Chemistry, University Hospital Munich-Grosshadern, Munich, Germany.

RESUMEN / SUMMARY: - Serum biomarkers are urgently needed for patient stratification and efficient treatment monitoring in pancreatic cancer (PC). Within a prospective diagnostic observation study, blood samples were obtained from 78 patients with advanced PC before and weekly during the course of palliative chemotherapy. Circulating nucleosomes and immunogenic cell death markers, high-mobility group box 1 (HMGB1), soluble receptors of advanced glycation end products (sRAGE) and DNase activity, were measured by enzyme-linked immunosorbent assay and correlated with results of radiological staging after 2 months of treatment, with time to progression (TTP) and overall survival (OS). Median TTP and OS of PC patients were 3.9 and 7.7 months, respectively. Pretherapeutic baseline biomarker levels did not correlate with objective response; however, nucleosome levels on day (d) 28 were higher ($p = 0.048$) and sRAGE levels at time of staging (d56) were lower in progressive patients ($p = 0.046$). Concerning estimation of prognosis, high nucleosome levels (d7, d14, d21 and d56), low sRAGE levels (d56) and DNase activity courses (d0-d7) correlated with TTP, whereas high nucleosomes (d7, d14 and d56), high HMGB1 (d21 and d56) and DNase (d0-d7) were associated with OS. After adjustment to Karnofsky performance score, nucleosomes and HMGB1 (both d56) and DNase (d0-d7) remained independent prognostic factors. Thus, courses of circulating nucleosomes and immunogenic cell death markers HMGB1 and sRAGE show prognostic relevance in PC patients undergoing chemotherapy.

[101]

TÍTULO / TITLE: - Fludarabine, cyclophosphamide and rituximab plus granulocyte macrophage colony-stimulating factor as frontline treatment for patients with chronic lymphocytic leukemia.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 29.

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

[3109/10428194.2013.819574](#)

AUTORES / AUTHORS: - Strati P; Ferrajoli A; Lerner S; O'Brien S; Wierda W; Keating MJ; Faderl S

INSTITUCIÓN / INSTITUTION: - Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

RESUMEN / SUMMARY: - Fludarabine, cyclophosphamide and rituximab (FCR), the standard of care for the frontline treatment of patients with chronic lymphocytic leukemia (CLL), is associated with a high rate of neutropenia and infectious complications. Granulocyte macrophage colony-stimulating factor

(GM-CSF) reduces myelosuppression and can potentiate rituximab activity. We conducted a clinical trial combining GM-CSF with FCR for frontline treatment of 60 patients with CLL. Eighty-six percent completed all six courses and 18% discontinued GM-CSF for toxicity: grade 3-4 neutropenia was observed in 30% of cycles, and severe infections in 16% of cases. The overall response rate was 100%. Both median event-free survival (EFS) and overall survival (OS) have not been reached. Longer EFS was associated with favorable cytogenetics. GM-CSF led to a lower frequency of infectious complications than in the historical FCR group, albeit similar EFS and OS.

[102]

TÍTULO / TITLE: - A Phase I Study of Quisinostat (JNJ-26481585), an Oral Hydroxamate Histone Deacetylase Inhibitor with Evidence of Target Modulation and Antitumor Activity, in Patients with Advanced Solid Tumors.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4262-72. doi: 10.1158/1078-0432.CCR-13-0312. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0312](#)

AUTORES / AUTHORS: - Venugopal B; Baird R; Kristeleit RS; Plummer R; Cowan R; Stewart A; Fourneau N; Hellemans P; Elsayed Y; McClue S; Smit JW; Forslund A; Phelps C; Camm J; Evans TR; de Bono JS; Banerji U

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow; The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust; UCL Cancer Institute; St. George's University of London, London; Northern Centre for Cancer Care, Freeman Hospital, Newcastle; The Christie NHS Foundation Trust, Manchester, United Kingdom; Janssen Research & Development, LLC, Beerse, Belgium; and Janssen Research & Development, LLC, Raritan, New Jersey.

RESUMEN / SUMMARY: - PURPOSE: To determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetic and pharmacodynamic profile of quisinostat, a novel hydroxamate, pan-histone deacetylase inhibitor (HDACi). EXPERIMENTAL DESIGN: In this first-in-human phase I study, quisinostat was administered orally, once daily in three weekly cycles to patients with advanced malignancies, using a two-stage accelerated titration design. Three intermittent schedules were subsequently explored: four days on/three days off; every Monday, Wednesday, Friday (MWF); and every Monday and Thursday (M-Th). Toxicity, pharmacokinetics, pharmacodynamics, and clinical efficacy were evaluated at each schedule. RESULTS: Ninety-two patients were treated in continuous daily (2-12 mg) and three intermittent dosing schedules (6-19 mg). Treatment-emergent adverse events included: fatigue, nausea, decreased appetite, lethargy, and vomiting. DLTs observed were predominantly cardiovascular, including nonsustained ventricular tachycardia,

ST/T-wave abnormalities, and other tachyarrhythmias. Noncardiac DLTs were fatigue and abnormal liver function tests. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) of quisinostat increased proportionally with dose. Pharmacodynamic evaluation showed increased acetylated histone 3 in hair follicles, skin and tumor biopsies, and in peripheral blood mononuclear cells as well as decreased Ki67 in skin and tumor biopsies. A partial response lasting five months was seen in one patient with melanoma. Stable disease was seen in eight patients (duration 4-10.5 months). CONCLUSIONS: The adverse event profile of quisinostat was comparable with that of other HDACi. Intermittent schedules were better tolerated than continuous schedules. On the basis of tolerability, pharmacokinetic predictions, and pharmacodynamic effects, the recommended dose for phase II studies is 12 mg on the MWF schedule. Clin Cancer Res; 19(15); 4262-72. ©2013 AACR.

[103]

TÍTULO / TITLE: - Thymidine kinase/ganciclovir and cytosine deaminase/5-fluorocytosine suicide gene therapy-induced cell apoptosis in breast cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 21. doi: 10.3892/or.2013.2562.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2562](#)

AUTORES / AUTHORS: - Kong H; Tao L; Qi K; Wang Y; Li Q; Du J; Huang Z

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Nan Shan District People's Hospital, Shenzhen, Guangdong 518052, P.R. China.

RESUMEN / SUMMARY: - The present study was conducted to explore the efficacy of suicide gene therapy with thymidine kinase (TK) in combination with cytosine deaminase (CD) for breast cancer. The expression of CD/TK was detected in the infected cells by RT-PCR. The killing effect on MCF-7 cells following treatment was analyzed by MTT assay. The morphological characteristics of the cells were observed by electron microscopy, and the distribution of the cell cycle was analyzed by flow cytometry. Caspase3 and -8 activities were detected by absorption spectrometry. Cytotoxic assays showed that cells transfected with CD/TK became more sensitive to the prodrugs. Morphological features characteristic of apoptosis were noted in the MCF7 cells via electron microscopy. The experimental data showed that the proportion of MCF-7 cells during the different phases of the cell cycle varied significantly following treatment with the prodrugs. The activity of caspase3 gradually increased following treatment with increasing concentrations of the prodrugs. We conclude that the TK/ganciclovir and CD/5-fluorocytosine suicide gene system used here induces apoptosis in breast cancer cells, and provides a promising treatment modality for breast cancer.

[104]

TÍTULO / TITLE: - The novel orally active proteasome inhibitor K-7174 exerts anti-myeloma activity in vitro and in vivo by down-regulating the expression of class I histone deacetylases.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jul 22.

●● Enlace al texto completo (gratis o de pago) 1074/jbc.M113.480574

AUTORES / AUTHORS: - Kikuchi J; Yamada S; Koyama D; Wada T; Nobuyoshi M; Izumi T; Akutsu M; Kano Y; Furukawa Y

INSTITUCIÓN / INSTITUTION: - Jichi Medical University, Japan;

RESUMEN / SUMMARY: - Bortezomib therapy is now indispensable for multiple myeloma, but is associated with patient inconvenience due to intravenous injection and emerging drug resistance. The development of orally active proteasome inhibitors with distinct mechanisms of action is therefore eagerly awaited. Previously, we identified homopiperazine derivatives as a novel class of proteasome inhibitors with a different mode of proteasome binding from bortezomib. In this study, we show that K-7174, one of proteasome-inhibitory homopiperazine derivatives, exhibits a therapeutic effect, which is stronger when administered orally than intravenously, without obvious side effects in a murine myeloma model. Moreover, K-7174 kills bortezomib-resistant myeloma cells carrying a beta5-subunit mutation in vivo and primary cells from a patient resistant to bortezomib. K-7174 induces transcriptional repression of class I histone deacetylases (HDAC1, 2 and 3) via caspase-8-dependent degradation of Sp1, the most potent transactivator of class I HDAC genes. HDAC1 overexpression ameliorates the cytotoxic effect of K-7174 and abrogates histone hyperacetylation without affecting the accumulation of ubiquitinated proteins in K-7174-treated myeloma cells. Conversely, HDAC inhibitors enhance the activity of K-7174 coincided with an increase in histone acetylation. These results suggest that class I HDACs are critical targets of K-7174-induced cytotoxicity. It is highly anticipated that K-7174 increases the tolerability and convenience of patients by oral administration and has the clinical utility in overcoming bortezomib resistance as a single agent or in combination with HDAC inhibitors.

[105]

TÍTULO / TITLE: - Wild-type Measles Virus Infection Upregulates Poliovirus Receptor-Related 4 and Causes Apoptosis in Brain Endothelial Cells by Induction of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand.

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

REVISTA / JOURNAL: - J Neuropathol Exp Neurol. 2013 Jul;72(7):681-96. doi: 10.1097/NEN.0b013e31829a26b6.

- Enlace al texto completo (gratis o de pago)

[1097/NEN.0b013e31829a26b6](https://doi.org/10.1097/NEN.0b013e31829a26b6)

AUTORES / AUTHORS: - Abdullah H; Brankin B; Brady C; Cosby SL

INSTITUCIÓN / INSTITUTION: - From the Centre for Infection and Immunity (HA, CB, SLC), School of Medicine Dentistry and Biomedical Sciences, Queen's University Belfast, UK; and School of Biological Sciences (BB), Dublin Institute of Technology, Dublin, Ireland.

RESUMEN / SUMMARY: - Small numbers of brain endothelial cells (BECs) are infected in children with neurologic complications of measles virus (MV) infection. This may provide a mechanism for virus entry into the central nervous system, but the mechanisms are unclear. Both in vitro culture systems and animal models are required to elucidate events in the endothelium. We compared the ability of wild-type (WT), vaccine, and rodent-adapted MV strains to infect, replicate, and induce apoptosis in human and murine brain endothelial cells (HBECs and MBECs, respectively). Mice also were infected intracerebrally. All MV strains productively infected HBECs and induced the MV receptor PVRL4. Efficient WT MV production also occurred in MBECs. Extensive monolayer destruction associated with activated caspase 3 staining was observed in HBECs and MBECs, most markedly with WT MV. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), but not Fas ligand, was induced by MV infection. Treatment of MBECs with supernatants from MV-infected MBEC cultures with an anti-TRAIL antibody blocked caspase 3 expression and monolayer destruction. TRAIL was also expressed in the endothelium and other cell types in infected murine brains. This is the first demonstration that infection of low numbers of BECs with WT MV allows efficient virus production, induction of TRAIL, and subsequent widespread apoptosis.

[106]

TÍTULO / TITLE: - Antitumor effects of chimeric receptor engineered human T cells directed to tumor stroma.

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

REVISTA / JOURNAL: - Mol Ther. 2013 Aug;21(8):1611-20. doi: 10.1038/mt.2013.110. Epub 2013 Jun 4.

- Enlace al texto completo (gratis o de pago) [1038/mt.2013.110](https://doi.org/10.1038/mt.2013.110)

AUTORES / AUTHORS: - Kakarla S; Chow KKh; Mata M; Shaffer DR; Song XT; Wu MF; Liu H; Wang LL; Rowley DR; Pfizenmaier K; Gottschalk S

INSTITUCIÓN / INSTITUTION: - 1] Center for Cell and Gene Therapy, Texas Children's Hospital, The Methodist Hospital, Baylor College of Medicine, Houston, Texas, USA [2] Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA [3] Interdepartmental Program in Translational Biology and Molecular Medicine, Baylor College of Medicine, Houston, Texas, USA.

RESUMEN / SUMMARY: - Cancer-associated fibroblasts (CAFs), the principle component of the tumor-associated stroma, form a highly protumorigenic and immunosuppressive microenvironment that mediates therapeutic resistance. Co-targeting CAFs in addition to cancer cells may therefore augment the antitumor response. Fibroblast activation protein-alpha (FAP), a type 2 dipeptidyl peptidase, is expressed on CAFs in a majority of solid tumors making it an attractive immunotherapeutic target. To target FAP-positive CAFs in the tumor-associated stroma, we genetically modified T cells to express a FAP-specific chimeric antigen receptor (CAR). The resulting FAP-specific T cells recognized and killed FAP-positive target cells as determined by proinflammatory cytokine release and target cell lysis. In an established A549 lung cancer model, adoptive transfer of FAP-specific T cells significantly reduced FAP-positive stromal cells, with a concomitant decrease in tumor growth. Combining these FAP-specific T cells with T cells that targeted the EphA2 antigen on the A549 cancer cells themselves significantly enhanced overall antitumor activity and conferred a survival advantage compared to either alone. Our study underscores the value of co-targeting both CAFs and cancer cells to increase the benefits of T-cell immunotherapy for solid tumors.

[107]

TÍTULO / TITLE: - Nuclear orphan receptor NR4A2 confers chemoresistance and predicts unfavorable prognosis of colorectal carcinoma patients who received postoperative chemotherapy.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jun 25. pii: S0959-8049(13)00461-9. doi: 10.1016/j.ejca.2013.06.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.06.001](#)

AUTORES / AUTHORS: - Han Y; Cai H; Ma L; Ding Y; Tan X; Liu Y; Su T; Yu Y; Chang W; Zhang H; Fu C; Cao G

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology, Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - BACKGROUND: NR4A2, an orphan nuclear receptor essential in neuron generation, has been recently linked to inflammatory and metabolic pathways of colorectal carcinoma (CRC). However, the effects of NR4A2 on chemo-resistance and postoperative prognosis of CRC remain unknown. METHODS: NR4A2 was transfected into CRC cells to investigate its effects on chemo-resistance to 5-fluorouracil and oxaliplatin and chemotherapeutics-induced apoptosis. We also investigated prostaglandin E2 (PGE2)-induced NR4A2 expression and its effect on chemo-resistance. Tissue microarrays including 51 adenoma, 14 familial adenomatous polyposis with CRC, 17 stage IV CRC with adjacent mucosa and 682 stage I-III CRC specimens were examined immunohistochemically for NR4A2 expression. Median follow-up time for stage I-III CRC patients was 53 months. RESULTS:

Ectopic expression of NR4A2 increased the chemo-resistance, and attenuated the chemotherapeutics-induced apoptosis. Transient treatment of PGE2 significantly up-regulated NR4A2 expression via protein kinase A pathway and increased the chemo-resistance. NR4A2 expression in epithelials consecutively increased from adenoma, adjacent mucosa to CRC (Ptrend<0.001). In multivariate Cox regression analyses, high NR4A2 expression in cancer nuclei (immunoreactive score4) significantly predicted a shorter disease-specific survival (DSS) of CRC patients (hazard ratio [HR]=1.88, P=0.024). High NR4A2 expression specifically predicted a shorter DSS of colon cancer patients (dichotomisation, HR=2.55, log-rank test P=0.011), especially for those who received postoperative 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX) chemotherapy (3-score range, HR=1.86, log-rank test P=0.020).
CONCLUSION: High expression of NR4A2 in CRC cells confers chemo-resistance, attenuates chemotherapeutics-induced apoptosis, and predicts unfavorable prognosis of colon cancer patients, especially for those who received postoperative chemotherapy. NR4A2 may be prognostic and predictive for colon cancer.

[108]

TÍTULO / TITLE: - Circulating miR-200c Levels Significantly Predict Response to Chemotherapy and Prognosis of Patients Undergoing Neoadjuvant Chemotherapy for Esophageal Cancer.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jul 10.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3093-](#)

[4](#)

AUTORES / AUTHORS: - Tanaka K; Miyata H; Yamasaki M; Sugimura K; Takahashi T; Kurokawa Y; Nakajima K; Takiguchi S; Mori M; Doki Y

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

RESUMEN / SUMMARY: - BACKGROUND: There is increasing evidence that microRNA expression in cancer tissue is useful for predicting the prognosis of patients with cancer. However, the relationship between the levels of circulating microRNAs and response to chemotherapy and prognosis remains unclear in esophageal cancer. METHODS: We measured the serum levels of miR-21, miR-145, miR-200c, and let-7c by quantitative RT-PCR in 64 patients with esophageal cancer who underwent neoadjuvant chemotherapy. RESULTS: The serum levels of miR-21, miR-145, miR-200c, and let-7c in esophageal cancer patients were significantly higher than those in healthy volunteers. High expression of miR-200c correlated significantly with poor response to chemotherapy (p = 0.0211). There was no significant relationship between chemosensitivity and the levels of miR-21, miR-145, and let-7c. High expression of miR-200c was associated with shortened progression-free survival (p =

0.0076), but there was no significant relationship between prognosis and the expression of miR-21, miR-145, and let-7c. Multivariate analysis identified miR-200c expression as the most valuable prognostic factor for patients with esophageal cancer who receive neoadjuvant chemotherapy. **CONCLUSIONS:** The serum level of miR-200c can be useful for predicting the response to chemotherapy and the prognosis of patients with esophageal cancer who receive neoadjuvant chemotherapy.

[109]

TÍTULO / TITLE: - 8-Oxo-7,8-dihydroguanine and uric acid as efficient predictors of survival in colon cancer patients.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 5. doi: 10.1002/ijc.28374.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28374](#)

AUTORES / AUTHORS: - Dziaman T; Banaszkiwicz Z; Roszkowski K; Gackowski D; Wisniewska E; Rozalski R; Foksinski M; Siomek A; Speina E; Winczura A; Marszalek A; Tudek B; Olinski R

INSTITUCIÓN / INSTITUTION: - Department of Clinical Biochemistry, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland.

RESUMEN / SUMMARY: - The aim of this work was to answer the question whether the broad range of parameters which describe oxidative stress and oxidatively damaged DNA and repair are appropriate prognosis factors of colon cancer (CRC) patients survival? The following parameters were analyzed for 89 CRC patients: concentration of uric acid and vitamins A, E, C in plasma; levels of 8-oxodGuo (8-oxo-7,8-dihydro-2'-deoxyguanosine) in DNA of leukocyte and colon tissues; urinary excretion rates of 8-oxodGuo and 8-oxoGua (8-oxo-7,8-dihydroguanine); the activity and mRNA or protein level of repair enzymes OGG1, APE1, ANPG, TDG and PARP1. All DNA modifications and plasma antioxidants were analyzed using high performance liquid chromatography (HPLC) or HPLC/gas chromatography-mass spectrometry techniques. Expression of repair proteins was analyzed by QPCR, Western or immunohistochemistry methods. Longer survival coincided with low levels of 8-oxodGuo/8oxoGua in urine and 8-oxodGuo in DNA as well as with high concentration of uric acid plasma level. In contrast to expectations, longer survival coincided with lower mRNA level in normal colon tissue of the main 8-oxoGua DNA glycosylase, OGG1, but no association was found for PARP-1 expression. When analyzing simultaneously two parameters the discriminating power increased significantly. Combination of low level of urinary 8-oxoGua together with low level of 8-oxodGuo in leukocyte (both below median value) or high concentration of plasma uric acid (above median value) have the best prediction power. Since prediction value of these parameters seems to be comparable to conventional staging procedure, they could possibly be used as markers to predict clinical success in CRC treatment.

[110]

TÍTULO / TITLE: - Omacetaxine mepesuccinate for patients with accelerated phase chronic myeloid leukemia with resistance or intolerance to two or more tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Haematologica. 2013 Jul;98(7):e78-9. doi: 10.3324/haematol.2012.083006. Epub 2013 Jun 10.

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

[3324/haematol.2012.083006](#)

AUTORES / AUTHORS: - Nicolini FE; Khoury HJ; Akard L; Rea D; Kantarjian H; Baccarani M; Leonoudakis J; Craig A; Benichou AC; Cortes J

INSTITUCIÓN / INSTITUTION: - franck-emmanuel.nicolini@chu-lyon.fr

[111]

TÍTULO / TITLE: - Targeting hyaluronic acid production for the treatment of leukemia: Treatment with 4-methylumbelliferone leads to induction of MAPK-mediated apoptosis in K562 leukemia.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Jul 19. pii: S0145-2126(13)00236-1. doi: 10.1016/j.leukres.2013.07.009.

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

[1016/j.leukres.2013.07.009](#)

AUTORES / AUTHORS: - Uchakina ON; Ban H; McKallip RJ

INSTITUCIÓN / INSTITUTION: - Division of Basic Medical Sciences, Mercer University School of Medicine, United States.

RESUMEN / SUMMARY: - The current study examined the effect of modulation of hyaluronic acid (HA) synthesis on leukemia cell survival using the hyaluronic acid synthesis inhibitor 4-methylumbelliferone (4-MU). Treatment of CML cells with 4-MU led to caspase-dependent apoptosis characterized by decreased HA production, PARP cleavage, and increased phosphorylation of p38. Addition of exogenous HA, the pan caspase inhibitor Z-VAD-FMK or the p38 inhibitor SB203580 to 4-MU treated cells was able to protect cells from apoptosis. Treatment of tumor-bearing mice with 4-MU led to a significant reduction in tumor load which was mediated through the induction of apoptosis.

[112]

TÍTULO / TITLE: - CYP2D6 Genotype Should Not Be Used for Deciding About Tamoxifen Therapy in Postmenopausal Breast Cancer.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Jul 20;31(21):2753-5. doi: 10.1200/JCO.2013.49.4278. Epub 2013 Jun 17.

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

[1200/JCO.2013.49.4278](https://doi.org/10.1200/JCO.2013.49.4278)

AUTORES / AUTHORS: - Rae JM; Regan M; Leyland-Jones B; Hayes DF; Dowsett M

INSTITUCIÓN / INSTITUTION: - Breast Oncology Program, Department of Internal Medicine, University of Michigan Medical Center, 1500 East Medical Center Dr, 6310 Cancer Center, Ann Arbor, MI 48109-5942; jimmyrae@umich.edu.

[113]

TÍTULO / TITLE: - Impact of hemochromatosis gene mutations on cardiac status in doxorubicin-treated survivors of childhood high-risk leukemia.

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

REVISTA / JOURNAL: - Cancer. 2013 Jul 16. doi: 10.1002/cncr.28256.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28256](https://doi.org/10.1002/cncr.28256)

AUTORES / AUTHORS: - Lipshultz SE; Lipsitz SR; Kutok JL; Miller TL; Colan SD; Neuberg DS; Stevenson KE; Fleming MD; Sallan SE; Franco VI; Henkel JM; Asselin BL; Athale UH; Clavell LA; Michon B; Laverdiere C; Larsen E; Kelly KM; Silverman LB

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Florida; Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, Florida.

RESUMEN / SUMMARY: - BACKGROUND: Doxorubicin is associated with progressive cardiac dysfunction, possibly through the formation of doxorubicin-iron complexes leading to free-radical injury. The authors determined the frequency of hemochromatosis (HFE) gene mutations associated with hereditary hemochromatosis and their relationship with doxorubicin-associated cardiotoxicity in survivors of childhood high-risk acute lymphoblastic leukemia. METHODS: Peripheral blood was tested for 2 common HFE allelic variants: C282Y and H63D. Serum cardiac troponin-T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP), which are biomarkers of cardiac injury and cardiomyopathy, respectively, were assayed during therapy. Left ventricular (LV) structure and function were assessed with echocardiography. RESULTS: A total of 184 patients had DNA results for at least 1 variant, and 167 had DNA results for both: 24% carried H63D and 10% carried C282Y. Heterozygous C282Y genotype was associated with multiple elevations in cTnT concentrations ($P = .039$), but not NT-proBNP. At a median of 2.2 years (range, 1.0 years-3.6 years) after diagnosis, the mean Z-scores for LV fractional shortening (-0.71 [standard error (SE), 0.25]; $P = .008$), mass (-0.84 [SE, 0.17]; $P < .001$), and end-systolic (-4.36 [SE, 0.26], $P < .001$) and end-diastolic (-0.68 [SE, 0.25]; $P = .01$) posterior wall thickness were found to be abnormal in children with either allele ($n = 32$). Noncarriers ($n = 63$) also were found to have

below-normal LV mass (-0.45 [SE, 0.15]; P = .006) and end-systolic posterior wall thickness (-4.06 [SE, 0.17]; P < .001). Later follow-up demonstrated similar results. CONCLUSIONS: Doxorubicin-associated myocardial injury was associated with C282Y HFE carriers. Although LV mass and wall thickness were found to be abnormally low overall, they were even lower in HFE carriers, who also had reduced LV function. Screening newly diagnosed cancer patients for HFE mutations may identify those at risk for doxorubicin-induced cardiotoxicity. Cancer 2013. © 2013 American Cancer Society.

[114]

TÍTULO / TITLE: - The role of human equilibrative nucleoside transporter 1 on the cellular transport of the DNA methyltransferase inhibitors, 5-azacytidine and CP-4200, in human leukemia cells.

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

REVISTA / JOURNAL: - Mol Pharmacol. 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) 1124/mol.113.086801

AUTORES / AUTHORS: - Hummel-Eisenbeiss J; Hascher A; Hals PA; Sandvold ML; Muller-Tidow C; Lyko F; Rius M

INSTITUCIÓN / INSTITUTION: - 1 German Cancer Research Center and German Cancer Consortium;

RESUMEN / SUMMARY: - The nucleoside analog 5-azacytidine is an archetypical drug for epigenetic cancer therapy and its clinical effectiveness has been demonstrated in the treatment of myelodysplastic syndromes (MDS) and acute myelogenous leukemia (AML). However, therapy resistance in patients with MDS/AML remains a challenging issue. Membrane proteins that are involved in drug uptake are potential mediators of drug resistance. The responsible proteins for the transport of 5-azacytidine into MDS/AML cells are unknown. We have now systematically analyzed the expression and activity of various nucleoside transporters. We identified the human equilibrative nucleoside transporter 1 (hENT1) as the most abundant nucleoside transporter in leukemia cell lines and in AML patient samples. Transport assays using [¹⁴C]5-azacytidine demonstrated Na⁺-independent uptake of the drug into the cells, which was inhibited by S-(4-nitrobenzyl)-6-thioinosine (NBTI), a hENT1 inhibitor. The cellular toxicity of 5-azacytidine and its DNA demethylating activity were strongly reduced after hENT1 inhibition. In contrast, the cellular activity of the 5-azacytidine derivative CP-4200, a nucleoside transporter independent drug, persisted after hENT1 inhibition. A strong dependence of 5-azacytidine-induced DNA demethylation on hENT1 activity was also confirmed by array-based DNA methylation profiling, which uncovered hundreds of loci that became demethylated only when hENT1-mediated transport was active. Our data establish hENT1 as a key transporter for the cellular uptake of 5-azacytidine in leukemia cells and raise the possibility that hENT1 expression might be a useful biomarker to predict the efficiency of 5-azacytidine treatments. Furthermore, our

data suggest that CP-4200 may represent a valuable compound for the modulation of transporter related 5-azacytidine resistances.

[115]

TÍTULO / TITLE: - Alterations in the expression pattern of MTHFR, DHFR, TYMS, and SLC19A1 genes after treatment of laryngeal cancer cells with high and low doses of methotrexate.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 10.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0960-](#)

[3](#)

AUTORES / AUTHORS: - Galbiatti AL; Castro R; Caldas HC; Padovani JA Jr; Pavarino EC; Goloni-Bertollo EM

INSTITUCIÓN / INSTITUTION: - Genetics and Molecular Biology Research Unit (UPGEM), Sao Jose do Rio Preto Medical School (FAMERP), Avenida Brigadeiro Faria Lima, n.5416, Sao Jose do Rio Preto, SP, Brazil, analivia_sg@yahoo.com.br.

RESUMEN / SUMMARY: - Inter-individual variations to methotrexate (MTX) outcome have been attributed to different expression profiles of genes related to folate metabolism. To elucidate the mechanisms of variations to MTX outcome, we investigated MTHFR, DHFR, TYMS, and SLC19A1 gene expression profiles by quantifying the mRNA level of the genes involved in folate metabolism to MTX response in laryngeal cancer cell line (HEP-2). For this, three different concentrations of MTX (0.25, 25, and 75 μmol) were added separately in HEP-2 cell line for 24 h at 37 degrees C. Apoptosis quantification was evaluated with fluorescein isothiocyanate-labeled Bcl-2 by flow cytometry. Real-time quantitative PCR technique was performed by quantification of gene expression with TaqMan® Gene Expression Assay. ANOVA and Bonferroni's post hoc tests were utilized for statistical analysis. The results showed that the numbers of apoptotic HEP-2 cells with 0.25, 25.0, and 75.0 μmol of MTX were 14.57, 77.54, and 91.58 %, respectively. We found that the expression levels for MTHFR, DHFR, TYMS, and SLC19A1 genes were increased in cells with 75.0 μmol of MTX ($p < 0.05$). Moreover, SLC19A1 gene presented lower expression in cells treated with 0.25 μmol of MTX ($p < 0.05$). In conclusion, our data suggest that MTHFR, DHFR, TYMS, and SLC19A1 genes present increased expression after the highest application of MTX dose in laryngeal cancer cell line. Furthermore, SLC19A1 gene also presents decreased expression after the lowest application of MTX dose in laryngeal cancer cell line. Significant alterations of expression of these studied genes in cell culture model may give support for studies in clinical practice and predict interesting and often novel mechanisms of resistance of MTX chemotherapy.

[116]

TÍTULO / TITLE: - Manipulating the Apoptotic Pathway: Potential Therapeutics for Cancer Patients.

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

REVISTA / JOURNAL: - Br J Clin Pharmacol. 2013 Jun 20. doi: 10.1111/bcp.12193.

●● Enlace al texto completo (gratis o de pago) [1111/bcp.12193](#)

AUTORES / AUTHORS: - Bates DJ; Lewis LD

RESUMEN / SUMMARY: - This review summarizes the current state of scientific understanding of the apoptosis pathway, with a focus on the proteins involved in the pathway, their interactions and functions. This forms the rationale for detailing the pre-clinical and clinical pharmacology of drugs that modulate the pivotal proteins in this pathway with emphasis on drugs that are furthest advanced in clinical development as anti-cancer agents. There is a focus on describing drugs that modulate three of the most promising targets in the apoptosis pathway namely; antibodies that bind and activate the death receptors; small molecules that inhibit the anti-apoptotic Bcl-2 family proteins; and small molecules and antisense oligonucleotides that inactivate the inhibitors of apoptosis (IAPs), all of which drive the equilibrium of the apoptotic pathway towards apoptosis. These structurally different yet functionally related groups of drugs represent a promising novel approach to anti-cancer therapeutics whether used as monotherapy or in combination with either classical cytotoxic or other molecularly targeted anti-cancer agents.

[117]

TÍTULO / TITLE: - Insights into the efficacy of golimumab plus methotrexate in patients with active rheumatoid arthritis who discontinued prior anti-tumour necrosis factor therapy: post-hoc analyses from the GO-AFTER study.

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

REVISTA / JOURNAL: - Ann Rheum Dis. 2013 Jul 29. doi: 10.1136/annrheumdis-2013-203435.

●● Enlace al texto completo (gratis o de pago) [1136/annrheumdis-2013-203435](#)

AUTORES / AUTHORS: - Smolen JS; Kay J; Matteson EL; Landewe R; Hsia EC; Xu S; Zhou Y; Doyle MK

INSTITUCIÓN / INSTITUTION: - Division of Rheumatology, Department of Medicine III, Medical University of Vienna, and 2nd Department of Medicine, Hietzing Hospital, Vienna, Austria.

RESUMEN / SUMMARY: - OBJECTIVE: Evaluate golimumab in patients with active rheumatoid arthritis (RA) and previous tumour necrosis factor-alpha (TNF) inhibitor use. METHODS: Patients (n=461) previously receiving ≥ 1 TNF inhibitor were randomised to subcutaneous injections of placebo, golimumab 50 mg or golimumab 100 mg q4 weeks. Primary endpoint ($\geq 20\%$

improvement in American College of Rheumatology (ACR20) criteria at week 14) findings have been reported for all patients in the trial. Reported herein are further assessments of efficacy/safety among patients receiving golimumab+methotrexate (MTX). RESULTS: Among efficacy-evaluable patients who received MTX at baseline, more receiving golimumab+MTX (n=201) than placebo+MTX (n=103) achieved ACR20 (40.8% vs 14.6%), ACR50 (20.9% vs 3.9%), and ACR70 (11.4% vs 2.9%) responses at week 24. Among the 137 patients who had received only one prior TNF inhibitor (adalimumab, n=33; etanercept, n=47; and infliximab, n=57), week 24 ACR20 rates were 30.3%, 46.8% and 50.9%, respectively, and thus lowest among those who previously used adalimumab. ACR20 response rates were 44.5% (61/137), 36.2% (17/47) and 23.5% (4/17) among patients who had received one, two or three TNF inhibitors, respectively. Adverse event (AE) rates were comparable across type/number of prior anti-TNF agents, but appeared somewhat higher among patients who discontinued previous TNF inhibitor(s) due to intolerance (37/49, 75.5%) versus lack of efficacy (LOE, 113/191, 59.2%). CONCLUSIONS: Patients with active RA previously treated with ≥ 1 TNF inhibitor had clinically relevant improvement with golimumab+MTX, which appeared somewhat enhanced among those who received only etanercept or infliximab as their prior TNF inhibitor. Golimumab+MTX safety appeared similar across patients, regardless of TNF inhibitor(s) previously used, with fewer AEs occurring among patients who discontinued prior therapy for LOE.

[118]

TÍTULO / TITLE: - Antitumor immune response of dendritic cells (DCs) expressing tumor-associated antigens derived from induced pluripotent stem cells: In comparison to bone marrow-derived DCs.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 3. doi: 10.1002/ijc.28367.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28367](#)

AUTORES / AUTHORS: - Iwamoto H; Ojima T; Hayata K; Katsuda M; Miyazawa M; Iida T; Nakamura M; Nakamori M; Iwahashi M; Yamaue H

INSTITUCIÓN / INSTITUTION: - Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama, 641-8510, Japan.

RESUMEN / SUMMARY: - It is generally accepted that the difficulty in obtaining a sufficient number of functional dendritic cells (DCs) is a serious problem in DC-based immunotherapy. Therefore, we used the induced pluripotent stem (iPS) cell-derived DCs (iPSDCs). If the therapeutic efficacy of iPSDCs is equivalent to that of bone marrow-derived DCs (BMDCs), then the aforementioned problems may be solved. In our study, we induced iPSDCs from iPS cells and examined the capacity for maturation of iPSDCs compared to that of BMDCs in addition to the capacity for migration of iPSDCs to regional lymph nodes. We adenovirally transduced the hgp100 gene, natural tumor antigens, into DCs and

immunized mice once with the genetically modified DCs. The cytotoxic activity of CD8 (+) cytotoxic T lymphocytes (CTLs) was assayed using a 51 Cr-release assay. The therapeutic efficacy of the vaccination was examined in a subcutaneous tumor model. Our results showed that iPSDCs have an equal capacity to BMDCs in terms of maturation and migration. Furthermore, hgp100-specific CTLs were generated in mice immunized with genetically modified iPSDCs. These CTLs exhibited as high a level of cytotoxicity against B16 cells as BMDCs. Moreover, vaccination with the genetically modified iPSDCs achieved as high a level of therapeutic efficacy as vaccination with BMDCs. Our study clarified experimentally that genetically modified iPSDCs have an equal capacity to BMDCs in terms of tumor-associated antigen-specific therapeutic antitumor immunity. This vaccination strategy may therefore be useful for future clinical application as a cancer vaccine.

[119]

TÍTULO / TITLE: - The p53 pathway induction is not primarily dependent on Ataxia Telangiectasia Mutated (ATM) gene activity after fludarabine treatment in chronic lymphocytic leukemia cells.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Aug;54(8):1840-3. doi: 10.3109/10428194.2013.796056. Epub 2013 Jul 1.

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

[3109/10428194.2013.796056](#)

AUTORES / AUTHORS: - Navrkalova V; Sebejova L; Zemanova J; Jaskova Z; Trbusek M

INSTITUCIÓN / INSTITUTION: - Department of Molecular Medicine, CEITEC - Central European Institute of Technology, Masaryk University , Brno , Czech Republic.

RESUMEN / SUMMARY: - Abstract The prognostic role of ATM defects is well documented in chronic lymphocytic leukemia. However, the predictive value of ATM inactivation is much less understood, even in response to common drugs like fludarabine. It has been demonstrated that CLL cells having inactive ATM exhibit defective phosphorylation of its downstream targets after fludarabine treatment. We performed alternative analysis focusing on fludarabine-induced p53 accumulation and induction of p53-downstream genes after artificial ATM inhibition and, in parallel, using cells with endogenous ATM inactivation. We show that after 24h fludarabine exposure: (i) 5 out of 8 ATM-deficient samples (63%) normally accumulated p53 protein, and (ii) all analyzed ATM-deficient samples (n = 7) manifested clear induction of p21, PUMA, BAX, and GADD45 genes. In all experiments, doxorubicin was used as a confined ATM inductor and confirmed effective ATM inactivation. In conclusion, CLL cells lacking functional ATM appear to have normal response to fludarabine regarding the p53 pathway activation.

[120]

TÍTULO / TITLE: - Cytarabine, Ki-67, and SOX11 in patients with mantle cell lymphoma receiving rituximab-containing autologous stem cell transplantation during first remission.

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

REVISTA / JOURNAL: - Cancer. 2013 Jun 17. doi: 10.1002/cncr.28219.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28219](#)

AUTORES / AUTHORS: - Chakhachiro ZI; Saliba RM; Okoroji GJ; Korbling M; Alousi AM; Betul O; Anderlini P; Ciurea SO; Popat U; Champlin R; Samuels BI; Medeiros LJ; Bueso-Ramos C; Khouri IF

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

RESUMEN / SUMMARY: - BACKGROUND: In the current study, the authors report the results of 39 patients with mantle cell lymphoma (MCL) who were treated with chemotherapy and high-dose rituximab-containing autologous stem cell transplantation (ASCT) during their first disease remission. METHODS: The median age of the patients was 54 years. At the time of diagnosis, 87% of patients had Ann Arbor stage IV disease, and 77% had bone marrow involvement. A Ki-67 level of > 30% was found in 11 of 27 patients (40%), and SOX11 (SRY [sex determining region Y]-box 11) expression was found to be positive in 17 of 18 patients (94%). Twenty-seven patients (69%) underwent induction therapy with high-dose cytarabine-containing chemotherapy. Rituximab was administered during stem cell collection at a dose of 1000 mg/m² on days +1 and +8 after ASCT. RESULTS: The estimated 4-year overall survival and progression-free survival rates were 82% and 59%, respectively. Twelve patients experienced disease recurrence. Fifteen of 16 patients who were alive and in complete remission at 36 months remained so at a median follow-up of 69 months (range, 38 months-145 months). The only determinant of recurrence risk found was a Ki-67 level of > 30%. Seven of 11 patients with a Ki-67 level > 30% experienced disease recurrence within the first 3 years versus only 3 of 16 patients with a Ki-67 level ≤ 30% (P = .02). Patients who received high-dose cytarabine did not have a significantly different risk of developing disease recurrence compared with other patients (P = .7). CONCLUSIONS: Administering ASCT with rituximab during stem cell collection and immediately after transplantation may induce a continuous long-term disease remission in patients with MCL with a Ki-67 level of ≤ 30%. Cancer 2013. © 2013 American Cancer Society.

[121]

TÍTULO / TITLE: - Prognostic impact of pERK in advanced hepatocellular carcinoma patients treated with sorafenib.

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

REVISTA / JOURNAL: - Eur J Surg Oncol. 2013 Jul 8. pii: S0748-7983(13)00428-9. doi: 10.1016/j.ejso.2013.06.018.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejso.2013.06.018](#)

AUTORES / AUTHORS: - Chen D; Zhao P; Li SQ; Xiao WK; Yin XY; Peng BG; Liang LJ

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary Surgery, First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan Road 2, Guangzhou 510080, Guangdong Province, China.

RESUMEN / SUMMARY: - **BACKGROUND:** Sorafenib represents the standard of care targeted therapy for patients with advanced hepatocellular carcinoma (HCC). However, biomolecules that predict a patient's response to sorafenib treatment for HCC remain largely unknown. Thus, this study was designed to investigate whether phosphorylated ERK (pERK) and members of the sorafenib target or PI3K/Akt/mTOR signaling pathway predict the efficacy of sorafenib in advanced HCC patients. **METHODOLOGY:** From December 2008 to October 2011, pathological specimens from 54 advanced HCC patients received sorafenib treatment were obtained. Clinicopathological variables, treatment response, survival and time to progression (TTP) were recorded. Immunophenotypical analysis was carried out using antibodies against pERK, phosphorylated S6K (pS6K), VEGFR2 and PTEN. **RESULTS:** The median overall survival (OS) and TTP were 14.2 and 3.4 months, respectively, and the disease control rate (DCR) was 59.3%. Better Eastern Cooperative Oncology Group Performance Status (ECOG PS) (95% CI: 3.27-4.93 m vs. 1.15-2.85 m, $p = 0.01$), Child-Pugh class A score (95% CI: 3.47-4.53 vs. 1.14-2.06 m, $p < 0.01$), and higher pERK (3.34-6.66 m vs. 1.33-2.67 m, $p = 0.03$) and VEGFR2 (3.49-6.52 m vs. 2.15-2.73 m, $p = 0.04$) immunohistochemical staining score were associated with increased TTP by univariate analysis. The ECOG PS ($p = 0.022$), Child-Pugh class ($p = 0.045$) and pERK staining score ($p = 0.012$) were found to be associated with TTP using multivariate analysis. **CONCLUSION:** Sorafenib treatment outcome is favorable in advanced HCC patients who received tumor resection and who have a good ECOG PS and Child-Pugh class A liver function. The pERK immunohistological staining score, ECOG PS and Child-Pugh class may be helpful in determining patients most likely to benefit from sorafenib therapy.

[122]

TÍTULO / TITLE: - Fish Oil Decreases C-Reactive Protein/Albumin Ratio Improving Nutritional Prognosis and Plasma Fatty Acid Profile in Colorectal Cancer Patients.

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

REVISTA / JOURNAL: - Lipids. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1007/s11745-013-3816-](https://doi.org/10.1007/s11745-013-3816-0)

[0](#)

AUTORES / AUTHORS: - Mocellin MC; Pastore E Silva JD; Camargo CD; Fabre ME; Gevaerd S; Naliwaiko K; Moreno YM; Nunes EA; Trindade EB

INSTITUCIÓN / INSTITUTION: - Post-Graduate Program of Nutrition, Department of Nutrition, Federal University of Santa Catarina, Reitor Joao David Ferreira Lima Campus, Trindade, Florianopolis, SC, 88040-970, Brazil, michel.mocellin@hotmail.com.

RESUMEN / SUMMARY: - Previous studies have shown that n-3 polyunsaturated fatty acids n-3 (n-3 PUFA) have several anticancer effects, especially attributed to their ability to modulate a variety of genomic and immune responses. In this context, this randomized, prospective, controlled clinical trial was conducted in order to check whether supplementation of 2 g/day of fish oil for 9 weeks alters the production of inflammatory markers, the plasma fatty acid profile and the nutritional status in patients with colorectal cancer (CRC). Eleven adults with CRC in chemotherapy were randomized into two groups: (a) supplemented (SG) daily with 2 g/day of encapsulated fish oil [providing 600 mg/day of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA)] for 9 weeks (n = 6), and (b) control (CG) (n = 5). All outcomes were evaluated on the day before the first chemotherapy session and 9 weeks later. Plasma TNF-alpha, IL-1beta, IL-10 and IL-17^a, the pro/anti-inflammatory balance (ratio TNF-alpha/IL-10 and IL-1beta/IL10) and serum albumin, showed no significant changes between times and study groups (p > 0.05). C-reactive protein (CRP) and the CRP/albumin ratio showed opposite behavior in groups, significantly reducing their values in SG (p < 0.05). Plasma proportions of EPA and DHA increased 1.8 and 1.4 times, respectively, while the ARA reduced approximately 0.6 times with the supplementation (9 weeks vs baseline, p < 0.05). Patients from SG gained 1.2 kg (median) while the CG lost -0.5 kg (median) during the 9 weeks of chemotherapy (p = 0.72). These results demonstrate that 2 g/day of fish oil for 9 weeks of chemotherapy improves CRP values, CRP/albumin status, plasma fatty acid profile and potentially prevents weight loss during treatment.

[123]

TÍTULO / TITLE: - Sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors in males, smokers, and non-adenocarcinoma lung cancer in patients with EGFR mutations.

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

REVISTA / JOURNAL: - Int J Biol Markers. 2013 Jul 18:0. doi: 10.5301/jbm.5000039.

●● Enlace al texto completo (gratis o de pago) [5301/jbm.5000039](https://doi.org/10.5301/jbm.5000039)

AUTORES / AUTHORS: - Zeng Z; Chen HJ; Yan HH; Yang JJ; Zhang XC; Wu YL

INSTITUCIÓN / INSTITUTION: - Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou - China.

RESUMEN / SUMMARY: -

Introduction: The demographical/clinical characteristics of being Asian, having an adenocarcinoma, being female, and being a “never-smoker” are regarded as favorable predictors for epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) efficacy in non-small cell lung cancer (NSCLC) with unknown EGFR gene status. In this study, we examined the effects of the supposedly unfavorable clinical variables in EGFR-mutant patients.

Method: In total, 159 EGFR-mutant NSCLC patients’ clinical features were correlated with progression-free survival (PFS), response rate (RR), and overall survival (OS). Multivariate analysis of clinical characteristics was performed using the Cox and logistic regression methods.

Result: There were 90 females (56.6%), 112 never-smokers (70.4%), and 153 patients with adenocarcinomas (96.2%). All patients were treated with EGFR-TKI, and 52.8% received TKI in a first-line setting. The median PFS of patients receiving first-line TKI was similar, regardless of gender (males vs females: 9.1 vs 9.7 months, $p=0.793$), smoking status (never-smokers vs smokers: 9.9 vs 9.1 months, $p=0.570$), or histology (adenocarcinoma vs non-adenocarcinoma: 9.7 vs 9.2 months, $p=0.644$). OS curves of first-line TKI-treated patients were also not associated with gender ($p=0.722$), smoking status ($p=0.579$), or histology ($p=0.480$). Similar results of PFS and OS were obtained for patients who received TKI beyond first-line. Multivariate analysis indicated that none of these clinical factors was an independent predictor of survival.

Conclusions: The supposedly ‘favorable’ clinical factors of female gender, non-smoking status, and adenocarcinoma were not independent predictive factors for PFS or OS in this population of EGFR-mutant NSCLC patients.

[124]

TÍTULO / TITLE: - Successful single-cycle rituximab treatment in a patient with pemphigus vulgaris and squamous cell carcinoma of the tongue and IgG antibodies to desmocollins.

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

REVISTA / JOURNAL: - J Am Acad Dermatol. 2013 Jul;69(1):e26-7. doi: 10.1016/j.jaad.2012.12.967.

●● Enlace al texto completo (gratis o de pago) [1016/j.jaad.2012.12.967](https://doi.org/10.1016/j.jaad.2012.12.967)

AUTORES / AUTHORS: - Kim J; Teye K; Koga H; Yeoh SC; Wakefield D; Hashimoto T; Murrell DF

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, St George Hospital, Sydney, Australia.

[125]

TÍTULO / TITLE: - Limited impact of prognostic factors in patients with recurrent glioblastoma multiforme treated with a bevacizumab-based regimen.

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

REVISTA / JOURNAL: - J Neurooncol. 2013 Jun 12.

- Enlace al texto completo (gratis o de pago) [1007/s11060-013-1170-](#)

[y](#)

AUTORES / AUTHORS: - Tabouret E; Barrie M; Thiebaut A; Matta M; Boucard C; Autran D; Loundou A; Chinot O

INSTITUCIÓN / INSTITUTION: - Department of Neuro-Oncology, Timone Hospital, APHM, 264, rue Saint Pierre, 13005, Marseille, France, emeline.tabouret@gmail.com.

RESUMEN / SUMMARY: - Bevacizumab has demonstrated activity in patients with recurrent glioblastoma. However, the impact of prognostic factors associated with recurrent glioblastoma treated with cytotoxic agents has not been determined in patients treated with bevacizumab. To analyze the prognostic factors and clinical benefits of bevacizumab and irinotecan treatment in patients with recurrent glioblastoma. This monocentric study retrospectively analyzed all patients with recurrent glioblastoma who were treated with at least one cycle of bevacizumab and irinotecan at our institution from April 2007 to May 2010. Multivariate analysis was used to analyze prognostic factors for overall survival (OS) from the initiation of bevacizumab administration. Among the 100 patients that were identified (M/F: 65/35), the median age was 57.9 years (range: 18-76). Karnofsky Performance Status (KPS) was <70 in 44 patients and ≥70 in 56 patients; 83 % of the patients were on steroids. The median tumor area was 2012 mm². The median progression free survival was 3.9 months (CI 95 %: 3.4-4.3). The median OS was 6.5 months (CI 95 %: 5.6-7.4). Multivariate analysis revealed that OS was affected by KPS (p = 0.024), but not by gender, age, steroid treatment, number of previous lines of treatment, tumor size, or time from initial diagnosis. KPS was improved in 30 patients, including 14/44 patients with an initial KPS <70. The median duration of maintained functional independence (KPS ≥70) was 3.75 months (CI 95 %: 2.9-4.6). The median OS from initial diagnosis was 18.9 months (CI 95 %: 17.5-20.3). In patients with recurrent glioblastoma treated with bevacizumab, KPS was revealed as the only factor to impact OS. The clinical benefits associated with this regimen appear valuable. A positive impact of bevacizumab administration on OS of patients with glioblastoma multiforme is suggested.

[126]

TÍTULO / TITLE: - High expression of M3 muscarinic acetylcholine receptor is a novel biomarker of poor prognostic in patients with non-small cell lung cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 10.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0982-](http://dx.doi.org/10.1007/s13277-013-0982-x)

[x](#)

AUTORES / AUTHORS: - Wu J; Zhou J; Yao L; Lang Y; Liang Y; Chen L; Zhang J; Wang F; Wang Y; Chen H; Ma J

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, the Third Affiliated Hospital, Harbin Medical University, Harbin, 150040, China.

RESUMEN / SUMMARY: - We assessed the expression of M3 receptor in non-small cell lung cancer (NSCLC) and determined its relationship with clinicopathological features and its impact on patient outcome. Specimens from 192 patients with NSCLC were investigated by immunohistochemistry for M3 receptor and Ki67 expression. Correlation between the expression of M3 receptor and Ki67 and various clinicopathological features of NSCLC patients was analyzed. We found that M3 receptor expression was gradually elevated from normal to metaplasia/dysplasia tissues to cancer tissues. Furthermore, there was a similar trend for Ki67 expression. Statistical analysis revealed that M3 receptor expression in tumor cells were correlated significantly with stage ($P < 0.0001$), histology type ($P = 0.0003$), Ki67 expression ($P < 0.0001$), tumor size ($P < 0.0001$), lymph node status ($P < 0.0001$), LVS invasion ($P = 0.0002$), and histology grade ($P < 0.0001$). Patients with M3 receptor high expression showed far lower disease-free survival (DFS) and overall survival (OS) rates than those with M3 receptor low expression. Multivariate Cox regression analysis demonstrated that high M3 receptor expression was an independent prognostic factor for both DFS and OS. High M3 receptor expression correlates with poor survival in NSCLC patients. M3 receptor expression may be related with tumor progression in NSCLC, indicating that M3 receptor may be a novel antineoplastic target in the future.

[127]

TÍTULO / TITLE: - High expression of lysine-specific demethylase 1 correlates with poor prognosis of patients with esophageal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 26;437(2):192-8. doi: 10.1016/j.bbrc.2013.05.123. Epub 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.123](http://dx.doi.org/10.1016/j.bbrc.2013.05.123)

AUTORES / AUTHORS: - Yu Y; Wang B; Zhang K; Lei Z; Guo Y; Xiao H; Wang J; Fan L; Lan C; Wei Y; Ma Q; Lin L; Mao C; Yang X; Chen X; Li Y; Bai Y; Chen D

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Institute of Surgery Research, Daping Hospital, The Third Military Medical University, Chongqing 400042, China.

RESUMEN / SUMMARY: - Recent studies have elucidated the role of lysine-specific demethylase 1 (LSD1), a member of the histone demethylases, in epigenetic regulation of tumor suppressing/promoting genes and neoplastic

growth. However, the expression of LSD1 in patients with esophageal squamous cell carcinoma (ESCC) is still unknown. Here, we reported that LSD1 expression was elevated in cancerous tissue and correlated with lymph node metastasis and poorer overall survival in patients with ESCC. Compared to EC109 cells, LSD1 expression was unregulated in aggressive cancer cell lines KYSE450 and KYSE150. Knockdown of LSD1 using lentivirus delivery of LSD1-specific shRNA abrogated the migration and invasion of ESCC cells in vitro. Further, a LSD1 inhibitor, tranilcypromine, suppressed H3K4me2 demethylation and attenuated cellular motility and invasiveness in a dose-dependent manner. Taken together, these data suggested that LSD1 was a potential prognostic maker and may be a molecular target for inhibiting invasion and metastasis in ESCC.

[128]

TÍTULO / TITLE: - Proteasome Inhibition by Bortezomib Increases IL-8 Expression in Androgen-Independent Prostate Cancer Cells: The Role of IKKalpha

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

REVISTA / JOURNAL: - J Immunol. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) 4049/jimmunol.1300895

AUTORES / AUTHORS: - Manna S; Singha B; Phyo SA; Gatla HR; Chang TP; Sanacora S; Ramaswami S; Vancurova I

INSTITUCIÓN / INSTITUTION: - Department of Biological Sciences, St. John's University, New York, NY 11439.

RESUMEN / SUMMARY: - Expression of the proinflammatory and proangiogenic chemokine IL-8, which is regulated at the transcriptional level by NF-kappaB, is constitutively increased in androgen-independent metastatic prostate cancer and correlates with poor prognosis. Inhibition of NF-kappaB-dependent transcription was used as an anticancer strategy for the development of the first clinically approved 26S proteasome inhibitor, bortezomib (BZ). Even though BZ has shown remarkable antitumor activity in hematological malignancies, it has been less effective in prostate cancer and other solid tumors; however, the mechanisms have not been fully understood. In this article, we report that proteasome inhibition by BZ unexpectedly increases IL-8 expression in androgen-independent prostate cancer PC3 and DU145 cells, whereas expression of other NF-kappaB-regulated genes is inhibited or unchanged. The BZ-increased IL-8 expression is associated with increased in vitro p65 NF-kappaB DNA binding activity and p65 recruitment to the endogenous IL-8 promoter. In addition, proteasome inhibition induces a nuclear accumulation of I kappa B kinase (IKK)alpha, and inhibition of IKKalpha enzymatic activity significantly attenuates the BZ-induced p65 recruitment to IL-8 promoter and IL-8 expression, demonstrating that the induced IL-8 expression is mediated, at least partly, by IKKalpha. Together, these data provide the first evidence, to our

knowledge, for the gene-specific increase of IL-8 expression by proteasome inhibition in prostate cancer cells and suggest that targeting both IKKalpha and the proteasome may increase BZ effectiveness in treatment of androgen-independent prostate cancer.

[129]

TÍTULO / TITLE: - Factors predicting long-term survival in colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1459-](http://1007/s00432-013-1459-4)

[4](#)

AUTORES / AUTHORS: - Huh JW; Kim CH; Lim SW; Kim HR; Kim YJ

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - **PURPOSE:** The aim of this study was to determine which clinicopathological factors influenced the long-term survival after potentially curative resection of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen (CEA). **METHODS:** A total of 1,732 patients who underwent curative surgery for primary nonmetastatic colorectal cancers from 1997 to 2009 were analyzed. Of these patients, 1,128 (65.1 %) had normal level of preoperative CEA (<5 ng/mL). The predicting factors for survival were analyzed. **RESULTS:** When the serum CEA cutoff value was set at 2.4 ng/mL (median value), the high CEA groups displayed a higher percentage of older patients, males, large-diameter tumors, advanced T and N categories, and positive perineural invasion, compared to the low CEA groups. Multivariate analysis revealed that age, T category, N category, number of lymph nodes retrieved, operative method, lymphovascular invasion, perineural invasion, postoperative chemotherapy, and preoperative serum CEA level ≥ 2.4 ng/mL were independent predictors for 5-year overall survival, while tumor location, tumor size, T category, N category, lymphovascular invasion, and perineural invasion were independent predictors for 5-year disease-free survival. **CONCLUSIONS:** Even if patients with colorectal cancer have a normal preoperative CEA before surgery, CEA may be useful for prognostic stratification using 2.4 ng/mL as the cutoff.

[130]

TÍTULO / TITLE: - A nanocarrier based on a genetically engineered protein cage to deliver doxorubicin to human hepatocellular carcinoma cells.

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

REVISTA / JOURNAL: - Chem Commun (Camb). 2013 Jul 25;49(67):7442-4. doi: 10.1039/c3cc44508a.

- Enlace al texto completo (gratis o de pago) [1039/c3cc44508a](#)

AUTORES / AUTHORS: - Toita R; Murata M; Abe K; Narahara S; Piao JS; Kang JH; Hashizume M

INSTITUCIÓN / INSTITUTION: - Department of Advanced Medical Initiatives, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. m-murata@dem.med.kyushu-u.ac.jp.

RESUMEN / SUMMARY: - Herein, we report the preparation of genetically engineered protein cages (HspG41C-SP94), taken up selectively by human hepatocellular carcinoma (HCC) cells. An engineered protein cage-doxorubicin (DOX) conjugate was as cytotoxic as free DOX against HCC cells but much less cytotoxic against normal hepatocytes.

[131]

TÍTULO / TITLE: - Serum Proteoglycans as Prognostic Biomarkers of Hepatocellular Carcinoma in Patients with Alcoholic Cirrhosis.

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

REVISTA / JOURNAL: - Cancer Epidemiol Biomarkers Prev. 2013 Aug;22(8):1343-1352. Epub 2013 Jun 18.

- Enlace al texto completo (gratis o de pago) [1158/1055-9965.EPI-13-0179](#)

AUTORES / AUTHORS: - Nault JC; Guyot E; Laguillier C; Chevret S; Ganne-Carrie N; N'kontchou G; Beaugrand M; Seror O; Trinchet JC; Coelho J; Lasalle P; Charnaux N; Delehedde M; Sutton A; Nahon P

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Service d'Hepatologie, Service de Biochimie, Service de Radiologie, Hopital Jean Verdier, AP-HP, Bondy; Universite Paris 13-UFR SMBH/INSERM U698, Bobigny; Inserm, UMR-674, Genomique fonctionnelle des tumeurs solides, IUH; Labex Immuno-oncology, Faculte de Medecine, Universite Paris Descartes, Sorbonne Paris Cite; Departement de Biostatistique, Hopital Saint-Louis, AP-HP; Unite de Biostatistique et Epidemiologie clinique, Universite Paris Diderot, INSERM, UMR-S717, Paris; Centre de Recherche Bichat Beaujon CRB3, Universite Paris 7, INSERM, U773, Paris; and Lunginnov Campus de l'Institut Pasteur de Lille, France.

RESUMEN / SUMMARY: - BACKGROUND: Proteoglycans are involved in neoangiogenesis and transduction of oncogenic signals, two hallmarks of carcinogenesis. METHODS: This study sought to assess the prognostic value of serum levels of three proteoglycans (endocan, syndecan-1, and glypican-3) and VEGF in 295 patients with alcoholic cirrhosis: 170 without hepatocellular carcinoma, 58 with early hepatocellular carcinoma, and 67 with advanced hepatocellular carcinoma at inclusion. We analyzed the association between proteoglycan levels and prognosis using Kaplan-Meier and Cox methods. RESULTS: Serum levels of the three proteoglycans and VEGF were increased in patients with advanced hepatocellular carcinoma compared with those

without hepatocellular carcinoma or with early hepatocellular carcinoma. In multivariate analysis, high levels of serum endocan (>5 ng/mL) were independently associated with death [HR, 2.84; 95% confidence interval (CI,) 1.18-6.84; P = 0.02], but not with hepatocellular carcinoma occurrence, in patients without hepatocellular carcinoma at baseline. High serum endocan (>5 ng/mL) and syndecan-1 (>50 ng/mL) levels were significantly associated with greater risk of tumor recurrence (P = 0.025) in patients with early hepatocellular carcinoma treated by radiofrequency ablation. In patients with advanced hepatocellular carcinoma, high serum levels of endocan (P = 0.004) and syndecan-1 (P = 0.006) were significantly associated with less favorable overall survival. However, only a high level of serum syndecan-1 (>50 ng/mL) was independently associated with greater risk of death (HR, 6.21 95% CI, 1.90-20.30; P = 0.0025). CONCLUSION: Serum endocan and syndecan-1 are easily assessable prognostic serum biomarkers of overall survival in alcoholic cirrhosis with and without hepatocellular carcinoma. IMPACT: These new biomarkers will be useful to manage patients with hepatocellular carcinoma developed on alcoholic cirrhosis. Cancer Epidemiol Biomarkers Prev; 22(8); 1343-52. ©2013 AACR.

[132]

TÍTULO / TITLE: - Recombinant GnRH-p53 protein sensitizes breast cancer cells to 5-fluorouracil-induced apoptosis in vitro and in vivo.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0863-](#)

[1](#)

AUTORES / AUTHORS: - Lu Y; Zhang Z; Yan Z; Chen L; Deng W; Lotze M; Wang Z; Lin X; Li LY

INSTITUCIÓN / INSTITUTION: - Nankai University College of Pharmacy and National Key Laboratory of Medicinal Chemical Biology, 94 Weijin Road, New Life Sciences Bldg A307, Tianjin, 300071, China.

RESUMEN / SUMMARY: - An ideal approach to treat cancers with dysfunctional p53 tumor suppressor gene is to reinstate p53 functionality by directly using p53 protein as a therapeutic agent. However, this has not been possible because the cells cannot readily internalize the protein. We constructed a fusion protein consisting of gonadotropin-releasing hormone (GnRH-p53) and p53 moieties. The recombinant protein was directly used to treat human breast cancer cells and athymic nude mice bearing breast cancer xenografts, with or without DNA synthesis-arresting agent 5-fluorouracil (5-FU). Treatments of cells from breast cancer cell-lines MDA-MB-231, T47D, or SKBR-3 with GnRH-p53 in combination with 5-FU significantly enhanced p53-activated apoptosis signals, including PUMA expression, BAX translocation to mitochondria, and activated caspase-3. Intratumoral injection of the GnRH-p53 protein inhibited MDA-MB-

231 xenograft growth and induced p53-mediated apoptosis in the tumors. Systemic treatment of the tumor-bearing mice via tail vein injection of GnRH-p53 markedly augmented the anticancer efficacy of 5-FU. Substitution of GnRH-p53 with wild type p53 protein had no effect. Recombinant GnRH-p53 is able to function as a surrogate of p53 with regard to its apoptosis-inducing activity. Combination of GnRH-p53 with DNA-damaging drugs may be of important therapeutic value for cancer treatment.

[133]

TÍTULO / TITLE: - Methionine Adenosyltransferase 2B, HuR and Sirtuin 1 Crosstalk Impacts on Resveratrol's Effect on Apoptosis and Growth in Liver Cancer Cells.

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

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

●● Enlace al texto completo (gratis o de pago) 1074/jbc.M113.487157

AUTORES / AUTHORS: - Yang H; Zheng Y; Li TW; Peng H; Fernandez Ramos D; Martinez-Chantar ML; Rojas AL; Mato JM; Lu SC

INSTITUCIÓN / INSTITUTION: - Keck School of Medicine of the University of Southern California, United States;

RESUMEN / SUMMARY: - Resveratrol is growth suppressive and pro-apoptotic in liver cancer cells. Methionine adenosyltransferase 2B (MAT2B) encodes for two dominant variant proteins V1 and V2 that positively regulate growth and V1 is anti-apoptotic when overexpressed. Interestingly crystal structure analysis of MAT2B protein (MATbeta) protomer revealed two resveratrol binding pockets, which raises the question of the role of MAT2B in resveratrol's biological activities. We found that resveratrol induced the expression of MAT2BV1 and V2 in a time and dose-dependent manner by increasing transcription, mRNA and protein stabilization. Following resveratrol treatment, HuR expression increased first, followed by SIRT1 and MAT2B. SIRT1 induction contributes to increased MAT2B transcription while HuR induction increased MAT2B mRNA stability. MATbeta interacts with HuR and SIRT1 and resveratrol treatment enhanced these interactions while reducing the interaction between MATbeta and MATbeta2. Since MATbeta lowers the K_i of MATbeta2 for S-adenosylmethionine (SAME), this allowed steady state SAME level to rise. Interaction between MATbeta, SIRT1 and HuR increased stability of these proteins. Induction of MAT2B is a compensatory response to resveratrol as knocking down MAT2BV1 potentiated resveratrol's pro-apoptotic and growth suppressive effects, while the opposite occurred with V1 overexpression. The same effect on growth occurred with MAT2BV2. In conclusion, resveratrol induces HuR, SIRT1 and MAT2B expression; the latter may represent a compensatory response against apoptosis and growth inhibition. However, MATbeta induction also facilitates SIRT1 activation, as the interaction stabilizes SIRT1. This complex interplay between MATbeta, HuR and SIRT1 has not been

previously reported and suggest these proteins may regulate each other's signaling.

[134]

TÍTULO / TITLE: - Combination of fludarabine, amsacrine, and cytarabine followed by reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation in patients with high-risk acute myeloid leukemia.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jun 1.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1790-](#)

[5](#)

AUTORES / AUTHORS: - Krejci M; Doubek M; Dusek J; Brychtova Y; Racil Z; Navratil M; Tomiska M; Horky O; Pospisilova S; Mayer J

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Masaryk University, Jihlavská 20, 625 00, Brno, Czech Republic, mkrejci@fnbrno.cz.

RESUMEN / SUMMARY: - Sequential use of chemotherapy and reduced-intensity conditioning (RIC) with allogeneic stem cell transplantation (SCT) has been proposed to improve the treatment outcomes in patients with high-risk acute myeloid leukemia (AML). Here, we present our experience with this procedure in a cohort of 60 AML patients with primary induction failure (n = 9); early, refractory, or \geq second relapse (n = 41); or unfavorable cytogenetics (n = 10). A combination of fludarabine (30 mg/m²/day), cytarabine (2 g/m²/day), and amsacrine (100 mg/m²/day) for 4 days was used. After 3 days of rest, RIC was carried out, consisting of 4 Gy total body irradiation, antithymocyte globulin (ATG-Fresenius), and cyclophosphamide (fludarabine, amsacrine, and cytarabine (FLAMSA)-RIC protocol). Prophylactic donor lymphocyte infusions (pDLIs) were given in patients with complete remission (CR) and without evidence of graft-versus-host disease \geq 120 days after SCT. The median time of neutrophil engraftment was 17 days. CR was achieved in 47 of 60 patients (78 %). Eleven patients received pDLIs resulting in long-term CR in eight of them. Non-relapse mortality after 1 and 3 years was 25 and 28 %, respectively. With a median follow-up of 37 months (range, 10-69), 3-year overall survival and 3-year progression-free survival were 42 and 33 %, respectively. In a multivariate analysis, dose of CD34(+) cells $>5 \times 10^6$ /kg (p = 0.005; hazard ratio (HR) = 0.276), remission of AML before SCT (p = 0.044; HR = 0.421), and achievement of complete chimerism after SCT (p = 0.001; HR = 0.205) were significant factors of better overall survival. The use of the FLAMSA-RIC protocol in suitable high-risk AML patients results in a long-term survival rate of over 40 %.

[135]

TÍTULO / TITLE: - Cessation of Tyrosine Kinase Inhibitors in Patients with Chronic-phase Chronic Myelogenous Leukemia Following Durable Complete Molecular Response: A Single Center Facing the Dilemma.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3509-14.

AUTORES / AUTHORS: - Iliakis T; Papadopoulou V; Diamantopoulos PT; Panayiotidis P; Zervakis K; Giannakopoulou N; Tilimidos G; Angelopoulou M; Siakantaris MP; Pangalis G; Mantzourani M; Variami E; Viniou NA

INSTITUCIÓN / INSTITUTION: - Correspondence to: Theodoros Iliakis, Hematology Unit, First Department of Internal Medicine, Laiko Hospital, University of Athens, 17 Agiou Thoma Street, Athens 11527, Greece. Tel: +30 2107456207, Fax: +30 2107788830.

RESUMEN / SUMMARY: - Tyrosine kinase inhibitors (TKIs), namely imatinib mesylate (IM) and recently approved second-generation TKIs dasatinib and nilotinib, are currently considered the treatment of choice for newly-diagnosed chronic phase chronic myelogenous leukemia (CP-CML). Although treatment with TKIs has not yet been proven curative, it certainly accomplishes a sustained control of the disease in the vast majority of patients. More than a decade after the successful launching of IM in first-line treatment of CP-CML and the subsequent introduction of second-generation TKIs in this setting, the question of the possibility of TKI cessation in a specific subset of patients has emerged. Side-effects of TKIs, along with some patients' wish to abandon the drugs and the rising financial burden upon healthcare systems, have led to the dilemma whether IM can be safely withdrawn after achieving deep molecular remissions and which patients are suitable for this discontinuation. We examined the data of our patients with CML in search of potential candidates for cessation of TKI therapy and identified their characteristics. We also performed a thorough review of the relevant literature. Eight out of fifty patients were discriminated on grounds of sustained complete molecular response (CMR) exceeding 12 months, most of them with a low or intermediate Sokal score at diagnosis. The median interval from IM initiation to CMR was almost 2 years and the median duration of detected CMR reached 6.5 years. Based on the promising results of prospective clinical trials reporting successful cessation of treatment with TKIs on selected subgroups of patients, we decided to proceed to interruption of therapy in the specific subset of our patients and closely monitor their response.

[136]

TÍTULO / TITLE: - Silencing of decoy receptor 3 (DcR3) expression by siRNA in pancreatic carcinoma cells induces Fas ligand-mediated apoptosis in vitro and in vivo.

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

REVISTA / JOURNAL: - Int J Mol Med. 2013 Sep;32(3):653-60. doi: 10.3892/ijmm.2013.1437. Epub 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1437](http://dx.doi.org/10.3892/ijmm.2013.1437)

AUTORES / AUTHORS: - Zhou J; Song S; He S; Wang Z; Zhang B; Li D; Zhu D

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006, P.R. China.

RESUMEN / SUMMARY: - Decoy receptor 3 (DcR3) is abundantly expressed in human tumors and protects cells from a wide range of apoptotic stimuli. In this study, we demonstrate that DcR3 is overexpressed in pancreatic carcinoma cells, and that the pancreatic carcinoma cell lines, Panc-1 and SW1990, are resistant to Fas ligand (FasL)-mediated apoptosis. To further define the function of DcR3 in cell growth and apoptosis, we used small interfering RNA (siRNA) to knockdown the expression of the DcR3 gene in Panc-1 and SW1990 cells. Our results revealed that the silencing of DcR3 expression enhanced the inhibitory effects of FasL and reduced the capability of the cells for proliferation and colony formation in vitro. In addition, the downregulation of DcR3 modulated the cell apoptotic regulators, Fas-associated death domain (FADD), caspase3 and caspase8, thus triggering cell apoptosis. Furthermore, the knockdown of DcR3 inhibited the growth of Panc-1 tumor xenografts. Taken together, our findings indicate that DcR3 is important in cancer progression and may be used as a potential therapeutic target for the gene therapy of pancreatic carcinoma.

[137]

TÍTULO / TITLE: - The Prognostic Value of Pathologic Prostate-specific Antigen Mass Ratio in Patients With Localized Prostate Cancer With Negative Surgical Resection Margins.

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

REVISTA / JOURNAL: - Urology. 2013 Jul 3. pii: S0090-4295(13)00567-0. doi: 10.1016/j.urology.2013.04.040.

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

[1016/j.urology.2013.04.040](http://dx.doi.org/10.1016/j.urology.2013.04.040)

AUTORES / AUTHORS: - Lee S; Jeong CW; Jeong SJ; Hong SK; Choi W; Byun SS; Lee SE

INSTITUCIÓN / INSTITUTION: - Department of Urology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

RESUMEN / SUMMARY: - **OBJECTIVE:** To investigate potential predictors of biochemical recurrence (BCR) in patients with localized prostate cancer with negative surgical resection margin (SRM). **MATERIALS AND METHODS:** Data from 582 consecutive patients diagnosed with localized prostate cancer with negative SRM who underwent only radical prostatectomy between November 2003 and April 2010 were reviewed. Pathologic prostate-specific antigen (PSA) mass ratio was defined as total circulating PSA protein per surgical prostate volume. Cox regression models tested the association between

clinicopathologic variables and BCR-free survival. RESULTS: Mean age at surgery was 64.9 +/- 6.9 years and mean PSA was 8.3 +/- 4.4 ng/mL. The mean follow-up period was 40.7 +/- 7.9 months. Pathologic stage was T2a in 113 of 582 patients (19.3%), T2b in 4 of 582 (0.7%), and T2c in 465 of 582 (79.9%). Surgical Gleason score was ≤ 6 in 215 of 582 patients (37.0%), 7 in 342 of 582 (58.8%), and ≥ 8 in 25 of 582 (4.3%). Mean pathologic prostate volume and pathologic PSA mass ratio were 42.4 +/- 15.8 mL (14.6-176.0 mL) and 0.48 +/- 0.37 mug/mL (0.03-2.62 mug/mL), respectively. Five-year BCR-free survival rate was 90.9%. PSA, surgical Gleason score, and pathologic PSA mass ratio were significantly associated with BCR-free survival in univariate analysis. In multivariate analysis, surgical Gleason score (P < .001, hazards ratio = 9.804) and pathologic PSA mass ratio (P = .037, hazards ratio = 3.753) were independent predictors of BCR-free survival. CONCLUSION: In patients with localized prostate cancer and negative SRM after radical prostatectomy, surgical Gleason score and pathologic PSA mass ratio were significant prognostic indicators of BCR-free survival.

[138]

TÍTULO / TITLE: - A novel anticancer agent Brousoflavonol B downregulates estrogen receptor (ER)-alpha36 expression and inhibits growth of ER-negative breast cancer MDA-MB-231 cells.

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

REVISTA / JOURNAL: - Eur J Pharmacol. 2013 Jun 11;714(1-3):56-64. doi: 10.1016/j.ejphar.2013.05.047.

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

[1016/j.ejphar.2013.05.047](#)

AUTORES / AUTHORS: - Guo M; Wang M; Deng H; Zhang X; Wang ZY

INSTITUCIÓN / INSTITUTION: - Department of Medical Microbiology and Immunology, Creighton University Medical School, 2500 California Plaza, Omaha, NE 68178, USA.

RESUMEN / SUMMARY: - Estrogen receptor (ER)-negative breast cancers are aggressive and unresponsive to antiestrogens, and current therapeutic modalities for ER-negative breast cancer patients are usually associated with strong toxicity and side effects. Less toxic and more effective targeted therapies are urgently needed to treat this type of breast cancer. Here, we report that Brousoflavonol B, a chemical purified from the bark of the Paper Mulberry tree (*Broussonetia papyrifera*) exhibited potent growth inhibitory activity in ER-negative breast cancer MDA-MB-231 cells at sub-micromolar concentrations. Brousoflavonol B induced cell cycle arrest at both the G0/G1 and G2/M phases accompanied by a downregulation of c-Myc protein, a upregulation of the cell cycle inhibitory proteins p16INK4a, p19INK4D and p21WAF1/CIP1 and a down-regulation of the expression levels of the G2/M regulatory proteins such as cyclin B1, cdc2 and cdc25C. Brousoflavonol B also induced apoptotic cell

death characterized by accumulation of the annexin V- and propidium iodide-positive cells, and cleavage of caspases 8, 9 and 3. In addition, Brousoflavonol B treatment also decreased the steady state levels of the epidermal growth factor receptor (EGFR) and ER-alpha36, a variant of estrogen receptor-alpha, and restricted growth of the stem-like cells in ER-negative breast cancer MDA-MB-231 cells. Our results thus indicate that Brousoflavonol B is a potent growth inhibitor for ER-negative breast cancer cells and provide a rationale for preclinical and clinical evaluation of Brousoflavonol B for ER-negative breast cancer therapy.

[139]

TÍTULO / TITLE: - Comparison of efficacy of 95-gene and 21-gene classifier (Oncotype DX) for prediction of recurrence in ER-positive and node-negative breast cancer patients.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jul;140(2):299-306. doi: 10.1007/s10549-013-2640-9. Epub 2013 Jul 25.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2640-](#)

[9](#)

AUTORES / AUTHORS: - Naoi Y; Kishi K; Tsunashima R; Shimazu K; Shimomura A; Maruyama N; Shimoda M; Kagara N; Baba Y; Kim SJ; Noguchi S

INSTITUCIÓN / INSTITUTION: - Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, 2-2-E10 Yamadaoka, Suita-shi, Osaka, 565-0871, Japan.

RESUMEN / SUMMARY: - We recently developed a 95-gene classifier (95(GC)) for the prognostic prediction for ER-positive and node-negative breast cancer patients treated with only adjuvant hormonal therapy. The aim of this study was to validate the efficacy of 95(GC) and compare it with that of 21(GC) (Oncotype DX) as well as to evaluate the combination of 95(GC) and 21(GC). DNA microarray data (gene expression) of ER-positive and node-negative breast cancer patients (n = 459) treated with adjuvant hormone therapy alone as well as those of ER-positive breast cancer patients treated with neoadjuvant chemotherapy (n = 359) were classified with 95(GC) and 21(GC) (Recurrence Online at <http://www.recurrenceonline.com/>). 95(GC) classified the 459 patients into low-risk (n = 285; 10 year relapse-free survival: 88.8 %) and high-risk groups (n = 174; 70.6 %) (P = 5.5e-10), and 21(GC) into low-risk group (n = 286; 89.3 %), intermediate-risk (n = 81; 75.7 %), and high-risk (n = 92; 64.7 %) groups (P = 2.9e-10). The combination of 95(GC) and 21(GC) classified them into low-risk (n = 324; 88.9 %) and high-risk (n = 135; 65.0 %) groups (P = 5.9e-14), and also showed that pathological complete response rates were significantly (P = 2.5e-6) higher for the high-risk (17.9 %) than the low-risk group (3.6 %). In addition, we demonstrated that 95(GC) was calculated on a single-sample basis if the reference robust multi-array average workflow was

used for normalization. The prognostic prediction capability of 95(GC) appears to be comparable to that of 21(GC). Moreover, their combination seems to result in the identification of more low-risk patients who do not need chemotherapy than either classification alone. The patients in the high-risk group were found to be more chemo-sensitive so that they can benefit more from adjuvant chemotherapy.

[140]

TÍTULO / TITLE: - Apoptosis-antagonizing transcription factor (AATF) gene silencing: role in induction of apoptosis and down-regulation of estrogen receptor in breast cancer cells.

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

REVISTA / JOURNAL: - Biotechnol Lett. 2013 Jun 26.

- Enlace al texto completo (gratis o de pago) [1007/s10529-013-1257-](#)

[8](#)

AUTORES / AUTHORS: - Sharma M

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology, Panjab University, Chandigarh, 160014, India, monika_sharma540@yahoo.com.

RESUMEN / SUMMARY: - Apoptosis-antagonizing transcription factor (AATF) is involved in transcriptional regulation, cell cycle control, DNA damage responses and in the execution of cell death programs. It also interacts directly with nuclear hormone receptors to enhance their transactivation. This study highlights the RNomics of AATF gene in the pathogenesis of breast cancer: RNA interference gave 64 % reduction in AATF mRNA and 47 % decline in AATF protein expression in MCF-7 breast cancer cells. Cell proliferation decreased by 41 % after transfection and was accompanied by apoptosis induction in 30 % MCF-7 cells. Pro-apoptotic genes (Bax, Bag4, Fas, Faslg, Fadd, Casp5, Casp6, Abl 1, Apaf1, Bcl2l 11, Card4, -6, -8, Bnip2 and Bnip3l) were up-regulated and anti-apoptotic genes (Bcl2, Mcl1dc, TNF, Pycard, Tradd, Bcl2A1 and Birc1) were down-regulated as were estrogen receptor mRNA (42 %) and protein expression (30 %). In normal non-malignant mammary epithelial cells (MCF-10^a) apoptosis induction was only 18 % with a 9 % fall in ER protein expression. Thus, AATF-silencing can be used to induce apoptosis and regulate ER expression in breast cancer cells for therapeutic interventions.

[141]

TÍTULO / TITLE: - KRAS Mutations in Advanced Nonsquamous Non-Small-Cell Lung Cancer Patients Treated with First-Line Platinum-Based Chemotherapy Have No Predictive Value.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Jun 19.

- Enlace al texto completo (gratis o de pago)

[1097/JTO.0b013e318298764e](https://doi.org/10.1097/JTO.0b013e318298764e)

AUTORES / AUTHORS: - Mellema WW; Dingemans AM; Thunnissen E; Snijders PJ; Derks J; Heideman DA; Van Suylen R; Smit EF

INSTITUCIÓN / INSTITUTION: - *Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, The Netherlands; daggerDepartment of Pulmonary Diseases and GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; double daggerDepartment of Pathology, VU University Medical Center, Amsterdam, The Netherlands; and section signDepartment of Pathology, Maastricht University Medical Center, Maastricht, The Netherlands.

RESUMEN / SUMMARY: - BACKGROUND:: Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is thought to be related with dismal outcome for non-small-cell lung cancer (NSCLC) patients. The role of KRAS mutation as a predictor of response to chemotherapy for patients with metastatic NSCLC is poorly understood. METHODS:: From a retrospective database of two university hospitals, all patients with advanced, nonsquamous NSCLC treated with first-line platinum-containing chemotherapy were selected. Mutation analysis for KRAS was performed and the relation with response to chemotherapy was assessed. Secondary endpoints were its relation with response to progression-free survival (PFS) and overall survival (OS). RESULTS:: A total of 161 patients, 94 men and 67 women, were included in this study. Median age was 60 years. The majority of patients (79%) had stage IV disease, of which 60 patients (37%) had a KRAS mutation. Patients with a KRAS mutation had a similar response to treatment as patients with KRAS wild-type (wt) ($p = 0.77$). Median PFS in KRAS-mutated patients was 4.0 months versus 4.5 months in KRAS wt patients (hazard ratio = 1.3; [95% confidence interval, 0.9-1.8]; $p = 0.16$). Median OS in patients with KRAS mutation was 7.0 months versus 9.3 months in patients with KRAS wt (hazard ratio = 1.2; [95% confidence interval, 0.9-1.7]; $p = 0.25$). Type of KRAS mutation had no influence on response or outcome. CONCLUSION:: On the basis of our multicenter data presented here, we conclude that KRAS mutation is not predictive for worse response to chemotherapy, PFS, and OS in advanced NSCLC patients treated with platinum-based chemotherapy in first-line setting.

[142]

TÍTULO / TITLE: - Antiestrogens suppress effects of transforming growth factor-beta in breast cancer cells via the signaling axis estrogen receptor-alpha and Y-box Binding Protein-1.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2473-80.

AUTORES / AUTHORS: - Popp SL; Joffroy C; Stope MB; Buck MB; Fritz P; Knabbe C

INSTITUCIÓN / INSTITUTION: - Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Multifunctional Y-box Binding Protein-1 (YB1) is correlated with a poor outcome in breast cancer. We found YB1 expression to be regulated by antiestrogens commonly used in the hormonal therapy of breast cancer and known as activators of Transforming Growth Factor-beta (TGFbeta). Thus, a putative influence of YB1 on TGFbeta signaling should be investigated. MATERIALS AND METHODS: The effect of YB1 on TGFbeta signaling was monitored by expression analysis and reporter gene assays in breast cancer cells overexpressing YB1 and treated with antiestrogens. RESULTS: Antiestrogen-mediated inhibition of estrogen receptor-alpha led to a suppression of YB1 protein synthesis. On the other hand, YB1 was found to be an enhancer of TGFbeta signaling. CONCLUSION: High levels of YB1 expression lead to a stimulation of TGFbeta pathways, thereby counteracting antihormonal breast cancer therapy and representing a putative resistance mechanism.

[143]

TÍTULO / TITLE: - Development of Acneiform Rash Does Not Predict Response to Lapatinib Treatment in Patients with Breast Cancer.

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

REVISTA / JOURNAL: - Pharmacotherapy. 2013 Jun 6. doi: 10.1002/phar.1308.

●● Enlace al texto completo (gratis o de pago) [1002/phar.1308](#)

AUTORES / AUTHORS: - Parma J; Pavlick A; Schiff R; Osborne CK; Chang JC; Rimawi M; Trivedi MV

INSTITUCIÓN / INSTITUTION: - University of Houston College of Pharmacy, Houston, Texas.

RESUMEN / SUMMARY: - STUDY OBJECTIVE: To determine if development of acneiform rash is a predictor of objective response rate with lapatinib. DESIGN: Subanalysis of data from a prospective, phase II study. SETTING: Academic breast care clinic. PATIENTS: Forty-nine treatment-naive patients with human epidermal growth factor receptor-2 (HER2)-positive locally advanced breast cancer, who were treated with neoadjuvant lapatinib monotherapy for 6 weeks; 47 patients were included in the final analysis. MEASUREMENTS AND MAIN RESULTS: Of the 49 patients enrolled, 33 (67%) developed a rash of any type, and 26 (55%) had acneiform rash. Of the 26 evaluable patients with acneiform rash (55%), 19 (73%) responded to lapatinib and 7 (27%) did not. Of the 21 evaluable patients without acneiform rash, 11 (67%) responded to treatment and 7 (33%) did not. Thus, no association was found between the occurrence of acneiform rash and response to lapatinib monotherapy. CONCLUSION: This study does not support the development of the acneiform rash as a predictor of clinical efficacy of lapatinib in the treatment of breast cancer.

[144]

TÍTULO / TITLE: - Retinoic acid plus arsenic trioxide, the ultimate panacea for acute promyelocytic leukemia?

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

REVISTA / JOURNAL: - Blood. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1182/blood-2013-06-505115](#)

AUTORES / AUTHORS: - Lallemand-Breitenbach V; de Thé H

INSTITUCIÓN / INSTITUTION: - Université Paris Diderot, Sorbonne Paris Cité, Hôpital St. Louis 1, Paris, France;

RESUMEN / SUMMARY: - Rarely in the field of cancer treatment did we experience as many surprises as with acute promyelocytic leukemia (APL). Yet, the latest clinical trial reported by Lo Coco et al in the New England Journal of Medicine is a practice-changing study, as it reports very favorable outcome of virtually all enrolled low-intermediate risk APL patients without any DNA-damaging chemotherapy¹. Although predicted from previous small pilot studies, these elegant and stringently controlled results open a new era in leukemia therapy.

[145]

TÍTULO / TITLE: - Common variants in genes coding for chemotherapy metabolizing enzymes, transporters, and targets: a case-control study of contralateral breast cancer risk in the WECARE Study.

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

REVISTA / JOURNAL: - Cancer Causes Control. 2013 Aug;24(8):1605-14. doi: 10.1007/s10552-013-0237-6. Epub 2013 Jun 18.

●● Enlace al texto completo (gratis o de pago) [1007/s10552-013-0237-6](#)

AUTORES / AUTHORS: - Brooks JD; Teraoka SN; Bernstein L; Møller M; Malone KE; Lynch CF; Haile RW; Concannon P; Reiner AS; Duggan DJ; Schiermeyer K; Bernstein JL; Figueiredo JC

INSTITUCIÓN / INSTITUTION: - Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, 307 E 63rd Street, 3rd Floor, New York, NY, USA, brooks.j@mskcc.org.

RESUMEN / SUMMARY: - PURPOSE: Women who receive chemotherapy for a first primary breast cancer have been observed to have a reduced risk of contralateral breast cancer (CBC), however, whether the genetic profile of a patient modifies this protective effect is currently not understood. The purpose of this study is to investigate the impact of germline genetic variation in genes coding for drug metabolizing enzymes, transporters, and targets on the association between chemotherapy and risk of CBC. METHODS: From the population-based Women's Environment Cancer and Radiation Epidemiology

(WECARE) Study, we included 636 Caucasian women with CBC (cases) and 1,224 women with unilateral breast cancer (controls). The association between common chemotherapeutic regimens, CMF and FAC/FEC, and risk of CBC stratified by genotype of 180 single nucleotide polymorphisms in 14 genes selected for their known involvement in metabolism, action, and transport of breast cancer chemotherapeutic agents, were determined using conditional logistic regression. RESULTS: CMF (RR = 0.5, 95 % CI 0.4, 0.7) and FAC/FEC (RR = 0.7, 95 % CI 0.4, 1.0) are associated with lower CBC risk relative to no chemotherapy in multivariable-adjusted models. Here we show that genotype of selected genes involved in the metabolism and uptake of these therapeutic agents does not significantly alter the protective effect of either CMF or FAC/FEC on risk of CBC. CONCLUSION: The results of this study show that germline genetic variation in selected gene does not significantly alter the protective effect of CMF, FAC, and FEC on risk of CBC.

[146]

TÍTULO / TITLE: - Early prediction of response to Sorafenib in patients with advanced hepatocellular carcinoma: the role of dynamic contrast enhanced ultrasound.

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

REVISTA / JOURNAL: - J Hepatol. 2013 Jun 25. pii: S0168-8278(13)00427-3. doi: 10.1016/j.jhep.2013.06.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.jhep.2013.06.011](#)

AUTORES / AUTHORS: - Assunta ZM; Matteo G; Andrea L; Enrico DS; Davide R; Elenora AB; Laura R; Elena AM; Francesca P; Gianluigi C; Lodovico RG; Raffaele L; Massimo S; Maurizio P; Antonio G

INSTITUCIÓN / INSTITUTION: - Dept. of Internal Medicine, Catholic University of Rome (Italy). Electronic address: mariaazocco@hotmail.com.

RESUMEN / SUMMARY: - BACKGROUND/AIMS: Sorafenib has become the standard first-line treatment for patients with advanced HCC and acts by inducing alterations in tumor vascularity. We wanted to evaluate the feasibility of dynamic CEUS (D-CEUS) as a predictor of early tumor response to Sorafenib and to correlate functional parameters with clinical efficacy endpoints.

METHODS: Twenty-eight HCC patients treated with Sorafenib 400 mg bid were prospectively enrolled. CEUS was performed at baseline (T0) and after 15 (T1) and 30 (T2) days of treatment. Tumor vasculature was assessed in a specific harmonic mode associated with a perfusion and quantification software (Q-Lab, Philips). Variations between T1/T2 and T0 were calculated for five D-CEUS functional parameters (peak intensity, PI; time to PI, TP; area under the curve, AUC; slope of wash in, Pw; mean transit time, MTT) and were compared for responders and non responders. The correlation between D-CEUS parameters, overall survival (OS) and progression free survival (PFS) was also assessed. A p value < 0.05 was considered statistically significant. RESULTS: The

percentage variation at T1 significantly correlated with response in three D-CEUS parameters (AUC, PI and Pw; $p = 0.002$, <0.001 and 0.003 respectively). A decrease of AUC ($p= 0.045$) and an increased/unchanged value of TP ($p=0.029$) and MTT ($p=0.010$) were associated with longer survival. Three D-CEUS parameters (AUC, TP, Pw) were significantly associated with PFS. CONCLUSION: D-CEUS provides a reliable and early measure of efficacy for anti-angiogenic therapies and could be an excellent tool for selecting patients who will benefit from treatment.

[147]

TÍTULO / TITLE: - Prognostic significance of nemo-like kinase (NLK) expression in patients with gallbladder cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0988-](#)

[4](#)

AUTORES / AUTHORS: - Li M; Zhang S; Wang Z; Zhang B; Wu X; Weng H; Ding Q; Tan Z; Zhang N; Mu J; Yang J; Shu Y; Bao R; Ding Q; Wu W; Cao Y; Liu Y

INSTITUCIÓN / INSTITUTION: - Research Institute of Biliary Tract Disease Affiliated to School of Medicine, Shanghai Jiao Tong University, No. 1665 Kongjiang Road, Shanghai, 200092, China.

RESUMEN / SUMMARY: - Nemo-like kinase (NLK), a serine/threonine protein kinase, has been implicated in tumor development and progression, and plays an important role in diverse signaling pathways by phosphorylating a variety of transcription factors. Recent studies demonstrated that altered expression of NLK was observed in various types of human cancers. However, the clinical significance of NLK expression in gallbladder cancer (GBC) remains largely unknown. In this study, we focused on the clinical significance of NLK in GBC, and found that nuclear NLK protein overexpression was frequently detected in GBC tissues. The overexpression of NLK was significantly correlated with histological grade, TNM stage, and perineural invasion. The results of Kaplan-Meier analysis indicated that a high expression level of NLK resulted in a significantly poorer prognosis of GBC patients ($P = 0.002$). Furthermore, multivariate Cox regression analysis showed that high NLK expression was an independent prognostic factor for GBC patients ($HR = 3.077$). In conclusion, overexpression of NLK is closely related to progression of GBC, and NLK could be used as a potential prognostic marker for GBC patients.

[148]

TÍTULO / TITLE: - Genetic variation in the PNPLA3 gene and hepatocellular carcinoma in USA: Risk and prognosis prediction.

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

REVISTA / JOURNAL: - Mol Carcinog. 2013 Jun 15. doi: 10.1002/mc.22057.

●● Enlace al texto completo (gratis o de pago) [1002/mc.22057](https://doi.org/10.1002/mc.22057)

AUTORES / AUTHORS: - Hassan MM; Kaseb A; Etzel CJ; El-Serag H; Spitz MR; Chang P; Hale KS; Liu M; Rashid A; Shama M; Abbruzzese JL; Loyer EM; Kaur H; Hassabo HM; Vauthey JN; Wray CJ; Hassan BS; Patt YZ; Hawk E; Soliman KM; Li D

INSTITUCIÓN / INSTITUTION: - Division of Cancer Medicine, Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

RESUMEN / SUMMARY: - Nonalcoholic fatty liver disease (NAFLD) is an emerging epidemic with high prevalence in Western countries. Genome-wide association studies had reported that a variation in the patatin-like phospholipase domain containing 3 (PNPLA3) gene is associated with high susceptibility to NAFLD. However, the relationship between this variation and hepatocellular carcinoma (HCC) has not been well established. We investigated the impact of PNPLA3 genetic variation (rs738409: C>G) on HCC risk and prognosis in the United States by conducting a case-control study that included 257 newly diagnosed and pathologically confirmed Caucasian patients with HCC (cases) and 494 healthy controls. Multivariate logistics and Cox regression models were used to control for the confounding effects of HCC risk and prognostic factors. We observed higher risk of HCC for subjects with a homozygous GG genotype than for those with CC or CG genotypes, the adjusted odds ratio (OR) was 3.21 (95% confidence interval [CI], 1.68-6.41). We observed risk modification among individuals with diabetes mellitus (OR = 19.11; 95% CI, 5.13-71.20). The PNPLA3 GG genotype was significantly associated with underlying cirrhosis in HCC patients (OR = 2.48; 95% CI, 1.05-5.87). Moreover, GG allele represents an independent risk factor for death. The adjusted hazard ratio of the GG genotype was 2.11 (95% CI, 1.26-3.52) compared with CC and CG genotypes. PNPLA3 genetic variation (rs738409: C>G) may determine individual susceptibility to HCC development and poor prognosis. Further experimental investigations are necessary for thorough assessment of the hepatocarcinogenic role of PNPLA3. © 2013 Wiley Periodicals, Inc.

[149]

TÍTULO / TITLE: - Polypeptide N-acetylgalactosaminyl transferase 3 independently predicts high-grade tumours and poor prognosis in patients with renal cell carcinomas.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 23;109(2):472-81. doi: 10.1038/bjc.2013.331. Epub 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.331](https://doi.org/10.1038/bjc.2013.331)

AUTORES / AUTHORS: - Kitada S; Yamada S; Kuma A; Ouchi S; Tasaki T; Nabeshima A; Noguchi H; Wang KY; Shimajiri S; Nakano R; Izumi H; Kohno K; Matsumoto T; Sasaguri Y

INSTITUCIÓN / INSTITUTION: - 1] Department of Pathology and Cell Biology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan [2] Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan.

RESUMEN / SUMMARY: - Background: The polypeptide N-acetylgalactosaminyltransferases (GalNAc-Ts) family of enzymes regulates the initial steps of mucin-type O-glycosylation. N-acetylgalactosaminyltransferases might show novel patterns of GalNAc-T glycosylation on tumour-derived proteins, which could influence cancer biology, but its mechanisms are unclear. We investigated the association of GalNAc-T3 and -T6 expressions with clinicopathological features and prognoses of patients with renal cell carcinomas (RCCs). Methods: Expressions of GalNAc-T3/6 and cell-adhesion molecules were analysed immunohistochemically in 254 paraffin-embedded tumour samples of patients with RCC. Results: Of 138 GalNAc-T3+ cases, 46 revealed significant co-expression with GalNAc-T6. N-acetylgalactosaminyltransferases-3+ expression showed a close relationship to poor clinical performance and large tumour size, or pathologically high Fuhrman's grading, and presence of vascular invasion and necrosis. The GalNAc-T3-positivity potentially suppressed adhesive effects with a significantly low beta-catenin expression. Univariate and multivariate analyses showed the GalNAc-T3+ group, but not the GalNAc-T6+ group, to have significantly worse survival rates. Conclusion: N-acetylgalactosaminyltransferases-3 expression independently predicts high-grade tumour and poor prognosis in patients with RCC, and may offer a therapeutic target against RCC.

[150]

TÍTULO / TITLE: - Combining CAR T cells and the Bcl-2 family apoptosis inhibitor ABT-737 for treating B-cell malignancy.

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

REVISTA / JOURNAL: - Cancer Gene Ther. 2013 Jul;20(7):386-93. doi: 10.1038/cgt.2013.35. Epub 2013 Jun 21.

●● Enlace al texto completo (gratis o de pago) [1038/cgt.2013.35](#)

AUTORES / AUTHORS: - Karlsson SC; Lindqvist AC; Fransson M; Paul-Wetterberg G; Nilsson B; Essand M; Nilsson K; Frisk P; Jernberg-Wiklund H; Loskog SI

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden.

RESUMEN / SUMMARY: - B-cell malignancies upregulate the B-cell lymphoma 2 (Bcl-2) family inhibitors of the intrinsic apoptosis pathway, making them therapy

resistant. However, small-molecule inhibitors of Bcl-2 family members such as ABT-737 restore a functional apoptosis pathway in cancer cells, and its oral analog ABT-263 (Navitoclax) has entered clinical trials. Gene engineered chimeric antigen receptor (CAR) T cells also show promise in B-cell malignancy, and as they induce apoptosis via the extrinsic pathway, we hypothesized that small-molecule inhibitors of the Bcl-2 family may potentiate the efficacy of CAR T cells by engaging both apoptosis pathways. CAR T cells targeting CD19 were generated from healthy donors as well as from pre-B-ALL (precursor-B acute lymphoblastic leukemia) patients and tested together with ABT-737 to evaluate apoptosis induction in five B-cell tumor cell lines. The CAR T cells were effective even if the cell lines exhibited different apoptosis resistance profiles, as shown by analyzing the expression of apoptosis inhibitors by PCR and western blot. When combining T-cell and ABT-737 therapy simultaneously, or with ABT-737 as a presensitizer, tumor cell apoptosis was significantly increased. In conclusion, the apoptosis inducer ABT-737 enhanced the efficacy of CAR T cells and could be an interesting drug candidate to potentiate T-cell therapy.

[151]

TÍTULO / TITLE: - Radioiodine therapy accelerates apoptosis in peripheral blood lymphocytes of patients with differentiated thyroid cancer.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(5):568-75. doi: 10.4149/neo_2013_074.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2013_074](#)

AUTORES / AUTHORS: - Vrndic O; Milosevic-Djordjevic O; Djurdjevic P; Jovanovic D; Mijatovic L; Jeftic I; Simonovic SZ

RESUMEN / SUMMARY: - Both apoptosis and micronuclei formation reflect cytogenetic damage in cells and could contribute to cell homeostasis. The aim of this study was to evaluate apoptosis in peripheral blood lymphocytes (PBLs) of patients with differentiated thyroid cancer (DTC) before and after 131-iodine (131-I)-therapy and its correlation with micronuclei (MN) frequency. The study population included 18 DTC patients and 18 healthy donors. Apoptotic cells were detected using the Annexin V-FITC/7-AAD kit and MN frequency by cytokinesis-block MN assay. The difference between early apoptosis in PBLs of DTC patients before therapy and controls (9.88 +/- 4.99% vs. 6.64 +/- 2.07%, p= 0.003) was significant, as well as between early apoptosis in PBLs of DTC patients before and after 131-I-therapy (9.88 +/- 4.99% vs. 13.53 +/- 6.57%, p= 0.008). The MN frequency and early apoptosis in PBLs of DTC patients was positively correlated before (r = 0.540, p= 0.021) and after 131-I-therapy (r=0.585, p= 0.014). Thyroid cancer patients had significantly increased early apoptosis in PBLs, which further increased after 131-I-therapy in association

with MN frequency. Keywords: apoptosis, differentiated thyroid cancer, micronuclei, peripheral blood lymphocytes, radioactive iodine.

[152]

TÍTULO / TITLE: - Bendamustine in chronic lymphocytic leukemia: outcome according to different clinical and biological prognostic factors in the everyday clinical practice.

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

REVISTA / JOURNAL: - Am J Hematol. 2013 Jul 16. doi: 10.1002/ajh.23546.

●● Enlace al texto completo (gratis o de pago) [1002/ajh.23546](#)

AUTORES / AUTHORS: - Francesco Z; Michael M; Volpetti S; Carlo V; Cinzia S; Ilaria N; Monica C; Achille A; Simona P; Renato F; Sergio C; Giovanni P; Livio T; Francesco R; Rossella P; Paolo V; Rosaria S; Isola M; Gianpietro S

INSTITUCIÓN / INSTITUTION: - Clinica Ematologica, DISM, Azienda Ospedaliero Universitaria S. M. Misericordia, Udine, Italy.

RESUMEN / SUMMARY: - Bendamustine proved to be effective for the treatment of chronic lymphocytic leukaemia (CLL). However, the relationship between its activity with clinico-biological prognosticators has been addressed only in few studies. We retrospectively evaluated the efficacy of bendamustine, in a real-life contest, on 142 patients, median age 70 years, median number of previous regimens 2 (0-8, 13% previously untreated). Bendamustine was administered for a median number of 4 cycles, in 84% of cases with rituximab. Overall (ORR) and complete response (CRR) rates were 68% and 16.5%, respectively. Multivariate analysis demonstrated a relationship between ORR and number of prior treatments (OR 0.25, 95% CI 0.08-0.71; P=0.009), del(17p) (OR 0.10, 95% CI 0.03-0.32; P <0.001) and concomitant rituximab (OR 4.37, 95% CI 1.12-17.04; P=0.033). The estimated 1- and 2-years overall survival (OS) and progression free survival (PFS) rates were 76%, 61%, 51% 26%, respectively. Previous sensitivity to fludarabine (HR 0.36, 95% CI 0.16-0.82), response to bendamustine (HR 0.21, 95% CI 0.10-0.45), and del(17p) (HR 2.18, 95% CI 1.002-4.74) had a prognostic significance in multivariate analysis for PFS, while the number of previous therapies (HR 3.48, 95% CI 1.29-9.38; P=0.014), concomitant use of rituximab (HR 0.32, 95% CI 0.11-0.93) and response to bendamustine (HR 0.22, 95% CI 0.07-0.66) were significant for OS. Side effects included grade 3-4 neutropenia, infections, thrombocytopenia and anemia which occurred in 40%, 14%, 14% and 10% of patients, respectively. These results confirm the activity and safety of bendamustine and rituximab combination even in patients with unfavourable clinical and biological features excluding del(17p).

[153]

TÍTULO / TITLE: - AKT-ing out: SGK kinases come to the fore.

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

REVISTA / JOURNAL: - Biochem J. 2013 Jun 15;452(3):e11-3. doi: 10.1042/BJ20130617.

●● Enlace al texto completo (gratis o de pago) [1042/BJ20130617](#)

AUTORES / AUTHORS: - Moniz LS; Vanhaesebroeck B

INSTITUCIÓN / INSTITUTION: - Centre for Cell Signalling, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK. I.moniz@qmul.ac.uk

RESUMEN / SUMMARY: - The success of targeted therapies in treating cancer over the last decade has been tempered by acquired drug resistance that follows long-term treatment. There is also emerging evidence for innate mechanisms of cancer cell resistance to targeted therapy that pre-exist as parallel signalling pathways. This aspect is explored by the Alessi group and collaborators from AstraZeneca in this issue of the Biochemical Journal, who identify a subset of breast cancer cell lines that are intrinsically resistant to Akt inhibition through constitutive up-regulation of the related AGC serine/threonine kinase SGK1 (serum- and glucocorticoid-regulated kinase 1). The study could help to profile tumours for sensitivity to Akt inhibitors and once more highlights the therapeutic complexity of cancer and the importance of exploring combination therapies in the clinic.

[154]

TÍTULO / TITLE: - Prophylactic post-transplant dasatinib administration in a pediatric patient with Philadelphia chromosome-positive acute lymphoblastic leukemia.

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

REVISTA / JOURNAL: - Pediatr Int. 2013 Jun;55(3):e56-8. doi: 10.1111/ped.12019.

●● Enlace al texto completo (gratis o de pago) [1111/ped.12019](#)

AUTORES / AUTHORS: - Watanabe A; Chansu S; Ogawa A; Asami K; Imamura M

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics, Niigata Cancer Center Hospital, Niigata, Japan.

RESUMEN / SUMMARY: - Philadelphia chromosome-positive acute lymphoblastic leukemia has a poor prognosis, even in pediatric patients. Although imatinib-containing chemotherapy can reportedly improve early event-free survival, allogeneic hematopoietic stem cell transplantation is still considered to be the main curative treatment option. Dasatinib, a novel abl tyrosine kinase inhibitor, is being used for the treatment of relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia and is reported to have excellent efficacy. We used dasatinib after bone marrow transplantation prior to the anticipated relapse for the purpose of prophylaxis against relapse. After discontinuation of dasatinib administration, molecular remission has lasted for 7 months. Although preventive use of dasatinib is as yet uncommon, we consider

that dasatinib may eradicate the minimal residual disease and prevent recurrence, and it is feasible to administer and appears to be safe. Further studies are needed to confirm our experience in this case.

[155]

TÍTULO / TITLE: - A phase II study of a personalized peptide vaccination for chemotherapy-resistant advanced pancreatic cancer patients.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 20. doi: 10.3892/or.2013.2556.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2556](#)

AUTORES / AUTHORS: - Yutani S; Komatsu N; Yoshitomi M; Matsueda S; Yonemoto K; Mine T; Noguchi M; Ishihara Y; Yamada A; Itoh K; Sasada T

INSTITUCIÓN / INSTITUTION: - Department of Immunology and Immunotherapy, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan.

RESUMEN / SUMMARY: - Pancreatic cancer is one of the most aggressive cancers with a median survival time (MST) of <6 months in chemotherapy-resistant patients. Therefore, the development of novel treatment modalities is needed. In the present study, a phase II study of personalized peptide vaccination (PPV) was conducted, in which vaccine antigens were selected and administered based on the pre-existing IgG responses to 31 different pooled peptides, for 41 chemotherapy-resistant advanced pancreatic cancer patients. No vaccine-related severe adverse events were observed. IgG responses specific to at least one of the vaccine peptides were augmented in 14 of 36 patients (39%) and in 18 of 19 patients (95%) tested after the 5th and 11th vaccination, respectively. MST from the first vaccination was 7.9 months with a 1-year survival rate of 26.8%. Higher serum amyloid A (SAA) and C-reactive protein (CRP) levels in pre-vaccination plasma were unfavorable factors for overall survival (OS). Due to the safety profile and the potential clinical efficacy, the conduction of additional clinical trials of PPV for chemotherapy-resistant advanced pancreatic cancer patients is warranted.

[156]

TÍTULO / TITLE: - CEA - a predictor for pathologic complete response after neoadjuvant therapy for rectal cancer.

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

REVISTA / JOURNAL: - Dis Colon Rectum. 2013 Jul;56(7):859-68. doi: 10.1097/DCR.0b013e31828e5a72.

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

[1097/DCR.0b013e31828e5a72](#)

AUTORES / AUTHORS: - Wallin U; Rothenberger D; Lowry A; Luepker R; Mellgren A

INSTITUCIÓN / INSTITUTION: - Division of Colon and Rectal Surgery, Department of Surgery, University of Minnesota, Minneapolis, Minnesota 52242, USA. ulrik-wallin@uiowa.edu

RESUMEN / SUMMARY: - **BACKGROUND:** Preoperative chemoradiation therapy in patients with rectal cancer results in pathologic complete response in approximately 10% to 30% of patients. Accurate predictive factors for obtaining pathologic complete response would likely influence the selection of patients best treated by chemoradiation therapy as the primary treatment without radical surgery. **OBJECTIVE:** The aim of this study was to evaluate the impact of tumor size, stage, location, circumferential extent, patient characteristics, and pretreatment CEA levels on the development of pathologic complete response after chemoradiation therapy. **DESIGN:** This study is a retrospective review. **SETTINGS AND PATIENTS:** Five hundred thirty patients treated with preoperative chemoradiation therapy and radical surgery for rectal adenocarcinoma between 1998 and 2011 were identified. A total of 469 patients remained after excluding patients with a history of pelvic radiation (n = 2), previous transanal endoscopic microsurgery or polypectomy of the primary lesion (n = 15), concurrent malignant tumor (n = 14), and no information about pre- or posttreatment T stage in the chart (n = 30). Preoperative CEA levels were available for 267 patients (57%). **INTERVENTIONS:** Preoperative chemoradiation therapy and total mesorectal excision were performed in patients with rectal cancer. **MAIN OUTCOME:** The primary outcome measured was pathologic complete response. **RESULTS:** : Ninety-six patients (20%) were found to have a pathologic complete response in the operative specimen. Low pretreatment CEA (3.4 vs 9.6 ng/mL; p = 0.008) and smaller mean tumor size (4.2 vs 4.7 cm; p = 0.02) were significantly associated with pathologic complete response. Low CEA levels and interruption in chemoradiation therapy were significant predictors of pathologic complete response in the multivariate analysis. When stratifying for smoking status, low CEA level was significantly associated with pathologic complete response only in the group of nonsmokers (p = 0.02). **LIMITATIONS:** This study was limited by its retrospective design, missing CEA values, and lack of tumor regression grade assessment. **CONCLUSIONS:** We demonstrated an association between low pretreatment CEA levels, interruption in chemoradiation therapy, and pathologic complete response in patients treated with neoadjuvant chemoradiation therapy for locally advanced rectal cancer. The predictive value of CEA in smokers can be limited, and further studies are needed to evaluate the impact of smoking on the predictive value of CEA levels for pathologic complete response in rectal cancer.

[157]

TÍTULO / TITLE: - Cytoreductive radiofrequency ablation in patients with metastatic renal cell carcinoma (RCC) with small primary tumours treated with sunitinib or interferon-alpha.

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

REVISTA / JOURNAL: - BJU Int. 2013 Jul;112(1):32-8. doi: 10.1111/bju.12107. Epub 2013 Jun 7.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12107](#)

AUTORES / AUTHORS: - Tsimafeyeu I; Zart JS; Chung B

INSTITUCIÓN / INSTITUTION: - Kidney Cancer Research Bureau, Moscow, Russian Federation. tsimafeyeu@kidneytumor.org

RESUMEN / SUMMARY: - **OBJECTIVES:** To evaluate the role of cytoreductive radiofrequency ablation (cRFA) in patients with metastatic renal cell carcinoma (RCC) with small primary tumours treated with immuno- or targeted therapy. To assess the efficacy of sunitinib in patients with metastatic RCC with unresected small primary tumours. **PATIENTS AND METHODS:** Three parallel single-arm prospective studies were conducted. Eligibility criteria were nearly identical for all trials and included: histopathologically confirmed RCC; metastatic measurable disease; size of primary tumour <5 cm; good or intermediate prognosis according to the Memorial Sloan-Kettering Cancer Center model; and no previous therapy. Study 1: Patients were treated with percutaneous cRFA under computed tomography guidance followed by interferon (IFN)-alpha, 9 MIU, s.c., three times per week. Study 2: Patients received cRFA followed by sunitinib in repeated 6-week cycles of 50 mg/day orally for 4 weeks, then 2 weeks off treatment. Study 3: Patients with unresected primary RCC received sunitinib alone. The primary endpoint was progression-free survival (PFS). **RESULTS:** Baseline patient characteristics (age, gender, histology, Eastern Cooperative Oncology Group performance status, metastatic sites, primary tumour size) were similar in all three studies. Efficacy data for 114 evaluable patients showed an objective response rate of 8% (95% confidence interval [CI] 4.5, 10.5) for study 1, 28.9% (95% CI 15.2, 34) for study 2, and 31.6% (95% CI 20.3, 38.9) for study 3. The median (95% CI) PFS times were 9.1 (6.9, 10.2), 13.4 (9.8, 14.4) and 12.7 (11.3, 13.5) months for studies 1, 2 and 3, respectively. Objective response rate was significantly higher and PFS significantly longer in the sunitinib trials than in study 1 ($P < 0.01$ all differences); no differences were found between studies 2 and 3 (objective response rate, $P = 0.1$; PFS, $P = 0.6$). Study 1 met its primary endpoint, showing that PFS was significantly longer than the expected 5 months ($P = 0.02$). The median (95% CI) objective survival (OS) times were greater in study 2 (cRFA/sunitinib) and study 3 (sunitinib-alone) than in study 1 (IFN-alpha) at 27.2 (22.6, 31.8) and 22.5 (20.7, 24.3) vs 19.5 (16.3, 22.7) months, respectively. Differences were significant (study 1 vs 2, hazard ratio [HR] = 0.55; $P = 0.003$; study 1 vs study 3 HR = 0.6, $P = 0.01$). OS was significantly longer in the cRFA/sunitinib group compared with the sunitinib-alone group (HR = 0.71; $P = 0.04$). There were no unexpected toxicities of medical treatment or

complications of cRFA. CONCLUSIONS: cRFA is a safe and effective approach for select patients with metastatic RCC treated with immunotherapy. The cRFA technique did not improve PFS in patients treated with sunitinib; cRFA probably has impact on OS in these patients. This needs to be tested in a larger trial. Sunitinib was effective in patients with metastatic RCC with unresected small primary tumours.

[158]

TÍTULO / TITLE: - Chemotherapy followed by modified donor lymphocyte infusion as a treatment for relapsed acute leukemia after haploidentical HSCT without in vitro T-cell depletion: superior outcomes compared with chemotherapy alone and an analysis of prognostic factors.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Jul 10. doi: 10.1111/ejh.12168.

●● [Enlace al texto completo \(gratis o de pago\) 1111/ejh.12168](#)

AUTORES / AUTHORS: - Yan CH; Wang JZ; Liu DH; Xu LP; Chen H; Liu KY; Huang XJ

INSTITUCIÓN / INSTITUTION: - Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, 100044, P.R.C.

RESUMEN / SUMMARY: - We retrospectively compared the anti-leukemic effects of chemotherapy alone and chemotherapy followed by modified donor lymphocyte infusion (DLI) in 82 patients with relapsed acute leukemia after haploidentical hematopoietic stem cell transplantation (HSCT) without in vitro T-cell depletion. We also investigated prognostic factors in patients receiving chemotherapy followed by modified DLI. Thirty-two patients received chemotherapy alone, and the remaining 50 patients received chemotherapy followed by modified DLI. In patients receiving chemotherapy followed by modified DLI, complete remission rate was significantly higher (64.0% vs. 12.5%, $P=0.000$), the incidence of relapse was significantly lower (50.0% vs. 100.0%, $P=0.000$), and disease-free survival was significantly improved (36.0% vs. 0.0%, $P=0.000$) compared with patients receiving chemotherapy alone. Multivariate analysis demonstrated that patients with chronic graft-versus-host disease (GVHD) after intervention ($P=0.000$) and patients receiving chemotherapy followed by modified DLI ($P=0.037$) were associated with a lower relapse rate. Furthermore, in patients receiving chemotherapy followed by modified DLI, multivariate analysis demonstrated that chronic GVHD after modified DLI ($P=0.039$) and duration of minimal residual disease (MRD) ($-$) \geq 4 months after modified DLI ($P=0.001$) were associated with a lower relapse rate. Our study is the first to suggest that chemotherapy followed by modified DLI is associated with stronger anti-leukemic effects and better survival in relapsed acute leukemia after haploidentical HSCT without in vitro T-cell depletion. Furthermore, our study suggests that lack of chronic GVHD and

duration of MRD (-) < 4 months after modified DLI are associated with higher relapse rates in patients receiving chemotherapy followed by modified DLI. This article is protected by copyright. All rights reserved.

[159]

TÍTULO / TITLE: - Concomitant Oral and Intravenous Pharmacokinetics of Dabrafenib, a BRAF Inhibitor, in Patients with BRAF V600 Mutation-Positive Solid Tumors.

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

REVISTA / JOURNAL: - J Clin Pharmacol. 2013 Sep;53(9):955-61. doi: 10.1002/jcph.127. Epub 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1002/jcph.127](#)

AUTORES / AUTHORS: - Denton CL; Minthorn E; Carson SW; Young GC; Richards-Peterson LE; Botbyl J; Han C; Morrison RA; Blackman SC; Ouellet D

INSTITUCIÓN / INSTITUTION: - GlaxoSmithKline, Research Triangle Park, NC, USA.

RESUMEN / SUMMARY: - Dabrafenib is an orally bioavailable, potent, and selective inhibitor of human wild-type BRAF and CRAF kinases as well as mutant forms of BRAF kinase. The aim of this phase 1, single-center, open-label study in four patients with BRAF mutation-positive solid tumors was to determine the absolute bioavailability of a 150 mg oral dose of dabrafenib. A microtracer study approach, in which a 50 microg radiolabeled intravenous (IV) microdose of dabrafenib was given concomitantly with a 150 mg oral dose, was used to simultaneously recover IV and oral pharmacokinetic parameters. The least squares mean (90% CI) absolute bioavailability of dabrafenib (HPMC capsules) was 94.5% (81.3%, 109.7%). Median T_{max} after oral administration was 2.0 hours and the geometric mean terminal half-life was 4.8 hours. The geometric mean clearance and volume of distribution after IV administration were 12.0 L/h and 45.5 L, respectively. Human clearance and volume of distribution at steady state were in agreement with predictions made using allometric scaling of pharmacokinetic parameters from four preclinical species. In conclusion, dabrafenib absolute bioavailability was high, whereas first-pass metabolism was low. Furthermore, the microtracer approach provided an innovative and efficient method for assessing the absolute bioavailability of dabrafenib in patients with advanced cancer.

[160]

TÍTULO / TITLE: - Early-onset neutropenia during perioperative chemotherapy is predictive of increased survival in patients with completely resected non-small cell lung cancer: a retrospective analysis.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2755-61.

AUTORES / AUTHORS: - Lee CY; Park SY; Shin TR; Park YB; Kim CH; Jang SH; Lee JW

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University, Anyang, Gyeonggi, Korea.

RESUMEN / SUMMARY: - BACKGROUND: Chemotherapy-induced neutropenia (CIN) has been found to be predictive of better therapeutic outcomes in studies of patients with various tumors. This study investigated whether CIN occurring during perioperative chemotherapy cycles 1 or 2 is a prognostic indicator in patients with completely resected non-small cell lung cancer (NSCLC). PATIENTS AND METHODS: The records of patients with completely resected NSCLC receiving at least two cycles of perioperative platinum-based doublet chemotherapy were reviewed retrospectively. Early-onset CIN was defined as a neutrophil count $<2.0 \times 10^9/l$ during chemotherapy cycles 1 or 2. Subjects were stratified into two groups: presence or absence of early-onset CIN. RESULTS: A total of 93 patients were included in this analysis. Early-onset CIN developed in 54.8% (51/93) cases. The median overall survival (OS) of patients developing early-onset CIN was significantly longer than the survival of patients without early-onset CIN (92.4 vs. 35.8 months, $p=0.022$), and the median disease-free survival (DFS) of patients with early-onset CIN was also longer, although the difference was not significant (48.3 vs. 18.6 months, $p=0.138$). Multivariate analysis demonstrated that early-onset CIN was an independent prognostic indicator for OS [hazard ratio (HR) for death=0.422, 95% confidence interval (CI)=0.201-0.884; $p=0.022$] and DFS (HR for recurrence=0.482, 95% CI=0.247-0.943; $p=0.033$). CONCLUSION: Early-onset CIN during perioperative chemotherapy is predictive of better OS and DFS in patients with completely resected NSCLC.

[161]

TÍTULO / TITLE: - Use of 5alpha-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: nationwide, population based case-control study.

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

REVISTA / JOURNAL: - BMJ. 2013 Jun 18;346:f3406. doi: 10.1136/bmj.f3406.

AUTORES / AUTHORS: - Robinson D; Garmo H; Bill-Axelsson A; Mucci L; Holmberg L; Stattin P

INSTITUCIÓN / INSTITUTION: - Department of Surgery and Perioperative Sciences, Umea University, 901 85 Umea, Sweden. drobinson@telia.com

RESUMEN / SUMMARY: - OBJECTIVE: To assess the association between 5alpha-reductase inhibitor (5-ARI) use in men with lower urinary tract symptoms and prostate cancer risk. DESIGN: Nationwide, population based case-control study for men diagnosed with prostate cancer in 2007-09 within the Prostate Cancer data Base Sweden 2.0. SETTING: The National Prostate Cancer Register, National Patient Register, census, and Prescribed Drug Register in

Sweden, from which we obtained data on 5-ARI use before date of prostate cancer diagnosis. PARTICIPANTS: 26,735 cases and 133,671 matched controls; five controls per case were randomly selected from matched men in the background population. 7815 men (1499 cases and 6316 controls) had been exposed to 5-ARI. 412 men had been exposed to 5-ARI before the diagnosis of a cancer with Gleason score 8-10. MAIN OUTCOME MEASURES: Risk of prostate cancer calculated as odds ratios and 95% confidence intervals by conditional logistic regression analyses. RESULTS: Risk of prostate cancer overall decreased with an increasing duration of exposure; men on 5-ARI treatment for more than three years had an odds ratio of 0.72 (95% confidence interval 0.59 to 0.89; P<0.001 for trend). The same pattern was seen for cancers with Gleason scores 2-6 and score 7 (both P<0.001 for trend). By contrast, the risk of tumours with Gleason scores 8-10 did not decrease with increasing exposure time to 5-ARI (for 0-1 year of exposure, odds ratio 0.96 (95% confidence interval 0.83 to 1.11); for 1-2 years, 1.07 (0.88 to 1.31); for 2-3 years, 0.96 (0.72 to 1.27); for >3 years, 1.23 (0.90 to 1.68); P=0.46 for trend). CONCLUSIONS: Men treated with 5-ARI for lower urinary tract symptoms had a decreased risk of cancer with Gleason scores 2-7, and showed no evidence of an increased risk of cancer with Gleason scores 8-10 after up to four years' treatment.

[162]

TÍTULO / TITLE: - Prognostic Role of Cell Cycle and Proliferative Biomarkers in Patients with Clear Cell Renal Cell Carcinoma.

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

REVISTA / JOURNAL: - J Urol. 2013 Jun 20. pii: S0022-5347(13)04648-X. doi: 10.1016/j.juro.2013.06.037.

●● Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.06.037](#)

AUTORES / AUTHORS: - Gayed BA; Youssef RF; Bagrodia A; Kapur P; Darwish OM; Krabbe LM; Sagalowsky A; Lotan Y; Margulis V

INSTITUCIÓN / INSTITUTION: - Department of Urology, University of Texas Southwestern Medical Center Dallas, TX.

RESUMEN / SUMMARY: - BACKGROUND: Cell cycle regulatory molecules are implicated in various stages of carcinogenesis. In this proof of principle study we systematically evaluate the association of aberrant expression of cell cycle regulators and proliferative markers on oncological outcomes of patients with clear cell renal carcinoma (ccRCC). MATERIALS AND METHODS: Immunohistochemistry for Cyclin D, Cyclin E, p16, p21, p27, p53, p57 and Ki67 was performed on tissue microarray constructs of 452 patients treated with extirpative therapy for ccRCC between 1997-2010. Clinical and pathologic data elements were collected. A prognostic marker score (MS) was defined as unfavorable if >4 biomarkers were altered. The relationship between MS and pathological features and oncological outcomes was evaluated. RESULTS:

Median age and follow up was 57 years (range 17-85) and 24 months (range 6-150), respectively. Unfavorable MS was found in 55 (12.2%) patients and was associated with adverse pathological features. A significant correlation between unfavorable MS and DFS (HR 26.62, 95% CI 43.38-100.04, p = 0.000) and with CSS (HR 8.15, 95% CI 74.42-101.56, p = 0.004) was demonstrated in Kaplan Meier survival analysis. In a multivariate analysis, unfavorable MS was an independent predictor of DFS (HR 2.63, CI 1.08-6.38, p = 0.033).

CONCLUSIONS: The cumulative number of aberrantly expressed cell cycle and proliferative biomarkers correlates with aggressive pathological features and inferior oncologic outcomes in patients with ccRCC. Our findings indicate that interrogation of cell cycle and proliferative markers is feasible and further prospective pathway-based exploration of biomarkers is needed.

[163]

TÍTULO / TITLE: - Subgroup-Specific Prognostic Implications of TP53 Mutation in Medulloblastoma.

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

REVISTA / JOURNAL: - J Clin Oncol. 2013 Aug 10;31(23):2927-35. doi: 10.1200/JCO.2012.48.5052. Epub 2013 Jul 8.

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

[1200/JCO.2012.48.5052](#)

AUTORES / AUTHORS: - Zhukova N; Ramaswamy V; Remke M; Pfaff E; Shih DJ; Martin DC; Castelo-Branco P; Baskin B; Ray PN; Bouffet E; von Bueren AO; Jones DT; Northcott PA; Kool M; Sturm D; Pugh TJ; Pomeroy SL; Cho YJ; Pietsch T; Gessi M; Rutkowski S; Bogner L; Klekner A; Cho BK; Kim SK; Wang KC; Eberhart CG; Fevre-Montange M; Fouladi M; French PJ; Kros M; Grajkowska WA; Gupta N; Weiss WA; Hauser P; Jabado N; Jouvett A; Jung S; Kumabe T; Lach B; Leonard JR; Rubin JB; Liao LM; Massimi L; Pollack IF; Shin Ra Y; Van Meir EG; Zitterbart K; Schuller U; Hill RM; Lindsey JC; Schwalbe EC; Bailey S; Ellison DW; Hawkins C; Malkin D; Clifford SC; Korshunov A; Pfister S; Taylor MD; Tabori U

INSTITUCIÓN / INSTITUTION: - Division of Haematology/Oncology, Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON M5G 1X8, Canada; uri.tabori@sickkids.ca.

RESUMEN / SUMMARY: - PURPOSE Reports detailing the prognostic impact of TP53 mutations in medulloblastoma offer conflicting conclusions. We resolve this issue through the inclusion of molecular subgroup profiles. PATIENTS AND METHODS We determined subgroup affiliation, TP53 mutation status, and clinical outcome in a discovery cohort of 397 medulloblastomas. We subsequently validated our results on an independent cohort of 156 medulloblastomas. Results TP53 mutations are enriched in wingless (WNT; 16%) and sonic hedgehog (SHH; 21%) medulloblastomas and are virtually absent in subgroups 3 and 4 tumors (P < .001). Patients with SHH/TP53 mutant

tumors are almost exclusively between ages 5 and 18 years, dramatically different from the general SHH distribution ($P < .001$). Children with SHH/TP53 mutant tumors harbor 56% germline TP53 mutations, which are not observed in children with WNT/TP53 mutant tumors. Five-year overall survival (OS; \pm SE) was 41% \pm 9% and 81% \pm 5% for patients with SHH medulloblastomas with and without TP53 mutations, respectively ($P < .001$). Furthermore, TP53 mutations accounted for 72% of deaths in children older than 5 years with SHH medulloblastomas. In contrast, 5-year OS rates were 90% \pm 9% and 97% \pm 3% for patients with WNT tumors with and without TP53 mutations ($P = .21$). Multivariate analysis revealed that TP53 status was the most important risk factor for SHH medulloblastoma. Survival rates in the validation cohort mimicked the discovery results, revealing that poor survival of TP53 mutations is restricted to patients with SHH medulloblastomas ($P = .012$) and not WNT tumors. CONCLUSION Subgroup-specific analysis reconciles prior conflicting publications and confirms that TP53 mutations are enriched among SHH medulloblastomas, in which they portend poor outcome and account for a large proportion of treatment failures in these patients.

[164]

TÍTULO / TITLE: - MiR-487^a resensitizes mitoxantrone (MX)-resistant breast cancer cells (MCF-7/MX) to MX by targeting breast cancer resistance protein (BCRP/ABCG2).

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jul 20. pii: S0304-3835(13)00536-3. doi: 10.1016/j.canlet.2013.07.016.

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

1016/j.canlet.2013.07.016

AUTORES / AUTHORS: - Ma MT; He M; Wang Y; Jiao XY; Zhao L; Bai XF; Yu ZJ; Wu HZ; Sun ML; Song ZG; Wei MJ

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, China Medical University, North 2nd Road 92, Heping District, Shenyang 110001, Liaoning Province, PR China.

RESUMEN / SUMMARY: - Breast cancer resistance protein (BCRP/ABCG2) specifically transports various chemotherapeutic agents and is involved in the development of multidrug resistance (MDR) in cancer cells. MicroRNAs (miRNAs) can play an important role in modulating the sensitivity of cancer cells to chemotherapeutic agents. Therefore, after confirming that BCRP was increased in the mitoxantrone (MX)-resistant MCF-7 breast cancer cell line MCF-7/MX compared with its parental sensitive MCF-7 cell line, we aimed to explore the miRNAs that regulate BCRP expression and sensitize breast cancer cells to chemotherapeutic agents. In the present study, bioinformatic analysis indicated that miR-487^a was one of the miRNAs that could bind to the 3' untranslated region (3'UTR) of BCRP. Quantitative RT-PCR (qRT-PCR)

analysis demonstrated that the expression of miR-487^a was reduced in MCF-7/MX cells, and a luciferase reporter assay demonstrated that miR-487^a directly bound to the 3'UTR of BCRP. Moreover, ectopic miR-487^a down-regulated BCRP expression at the mRNA and protein levels, increasing the intracellular accumulation and cytotoxicity of MX in resistant MCF-7/MX breast cancer cells. Meanwhile, inhibition of miR-487^a increased BCRP expression at the mRNA and protein levels and induced MX resistance in sensitive MCF-7 breast cancer cells. Furthermore, the reduced expression of BCRP and increased antitumor effects of MX were also detected in MCF-7/MX xenograft tumors treated with the miR-487^a agmir. Thus, our results suggested that miR-487^a can directly regulate BCRP expression and reverse chemotherapeutic drug resistance in a subset of breast cancers.

[165]

TÍTULO / TITLE: - Integrin alpha 7 Binds Tissue Inhibitor of Metalloproteinase 3 to Suppress Growth of Prostate Cancer Cells.

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

REVISTA / JOURNAL: - Am J Pathol. 2013 Jul 2. pii: S0002-9440(13)00396-9. doi: 10.1016/j.ajpath.2013.05.010.

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

1016/j.ajpath.2013.05.010

AUTORES / AUTHORS: - Tan LZ; Song Y; Nelson J; Yu YP; Luo JH

INSTITUCIÓN / INSTITUTION: - Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

RESUMEN / SUMMARY: - Integrin alpha7 (ITGA7) is a tumor-suppressor gene that is critical for suppressing the growth of malignant tumors; however, the mechanisms allowing ITGA7 to suppress the growth of cancer cells remain unclear. Herein, we show that ITGA7 binds to tissue inhibitor of metalloproteinase 3 (TIMP3) in prostate cancer cells. The ITGA7-TIMP3 binding led to a decreased protein level of tumor necrosis factor alpha, cytoplasmic translocation of NF-kappaB, and down-regulation of cyclin D1. These changes led to an accumulation of cells in G0/G1 and a dramatic suppression of cell growth. Knocking down TIMP3 or ITGA7/TIMP3 binding interference largely abrogated the signaling changes induced by ITGA7, whereas a mutant ITGA7 lacking TIMP3 binding activity had no tumor-suppressor activity. Interestingly, knocking down ITGA7 ligand laminin beta1 enhanced ITGA7-TIMP3 signaling and the downstream tumor-suppressor activity, suggesting the existence of a counterbalancing role between extracellular matrix and integrin signaling. As a result, this report demonstrates a novel and critical signaling mechanism of ITGA7, through the TIMP3/NF-kappaB/cyclin D1 pathway.

[166]

TÍTULO / TITLE: - p53siRNA therapy reduces cell proliferation, migration and induces apoptosis in triple negative breast cancer cells.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Sep;381(1-2):61-8. doi: 10.1007/s11010-013-1688-5. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1688-](#)

[5](#)

AUTORES / AUTHORS: - Braicu C; Pileczki V; Irimie A; Berindan-Neagoe I

INSTITUCIÓN / INSTITUTION: - Research Center for Functional Genomics, Biomedicine and Translational Medicine, “Iuliu Hatieganu” University of Medicine and Pharmacy, Victor Babes, Cluj-Napoca, Romania, braicucornelia@yahoo.com.

RESUMEN / SUMMARY: - p53 protein is probably the best known tumor suppressor. Earlier reports proved that human breast cancer cells expressing mutant p53 displayed resistance to apoptosis. This study is intended to investigate, the potential applications of RNA interference (RNAi) to block p53 expression, as well as its subsequent effect on cell growth, apoptosis and migration on a triple negative human breast cancer cell line (Hs578T). p53siRNA significantly reduced cell index (CI) compared to the control and we observed an inhibition of cellular migration in the interval of time between 0 and 30 h, as shown in the data obtained by dynamic evaluation using the xCELLigence System. Also, by using PCR-array technology, a panel of 84 key genes involved in apoptosis was investigated. Our studies indicate that the knockdown of p53 expression by siRNA modulates several genes involved in cell death pathways and apoptosis, showing statistically significant gene expression differences for 22 genes, from which 18 were upregulated and 4 were downregulated. The present research also emphasizes the important role of BCL-2 pro-apoptotic family of genes (Bim, Bak, and Bax) in activating apoptosis and reducing cell proliferation by p53siRNA treatment. Death receptors cooperate with BCL-2 pro-apoptotic genes in reducing cell proliferation. The limited success may be due to the activation of the antiapoptotic gene Mcl-1, and it may be associated with the resistance of triple negative breast cancer cells to cancer treatment. Thus, targeting p53siRNA pathways using siRNA may serve as a promising therapeutic strategy for the treatment of breast cancers.

[167]

TÍTULO / TITLE: - B-cell lymphoma in a patient with complete interferon gamma receptor 1 deficiency.

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

REVISTA / JOURNAL: - J Clin Immunol. 2013 Aug;33(6):1062-6. doi: 10.1007/s10875-013-9907-0. Epub 2013 Jun 26.

- Enlace al texto completo (gratis o de pago) [1007/s10875-013-9907-](https://doi.org/10.1007/s10875-013-9907-0)

[0](#)

AUTORES / AUTHORS: - Bax HI; Freeman AF; Anderson VL; Vesterhus P; Laerum D; Pittaluga S; Wilson WH; Holland SM

INSTITUCIÓN / INSTITUTION: - Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, h.bax@erasmusmc.nl.

RESUMEN / SUMMARY: - Immunosuppression-associated lymphoproliferative disorders can be related to primary as well as acquired immune disorders. Interferon gamma receptor (IFN-gammaR) deficiency is a rare primary immune disorder, characterized by increased susceptibility to mycobacterial infections. Here we report the first case of an Epstein Barr Virus (EBV) related B-cell lymphoma in a patient with complete IFN-gammaR1 deficiency. The patient was a 20-year-old man with homozygous 22Cdel in IFNGR1 resulting in complete absence of IFN-gammaR1 surface expression and complete lack of responsiveness to IFN-gamma in vitro. He had disseminated refractory Mycobacterium avium complex and Mycobacterium abscessus infections. At age 18 he presented with new spiking fever and weight loss that was due to an EBV-positive B-cell non-Hodgkin lymphoma. Two years later he died of progressive lymphoma. IFN-gamma plays an important role in tumor protection and rejection. Patients with IFN-gammaR deficiencies and other immune deficits predisposing to mycobacterial disease seem to have an increased risk of malignancies, especially those related to viral infections. As more of these patients survive their early infections, cancer awareness and tumor surveillance may need to become a more routine part of management.

[168]

TÍTULO / TITLE: - The predictive value of serum soluble E-cadherin levels in breast cancer patients undergoing preoperative systemic chemotherapy.

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

REVISTA / JOURNAL: - Clin Biochem. 2013 Jun 18. pii: S0009-9120(13)00287-7. doi: 10.1016/j.clinbiochem.2013.06.010.

- Enlace al texto completo (gratis o de pago)

[1016/j.clinbiochem.2013.06.010](https://doi.org/10.1016/j.clinbiochem.2013.06.010)

AUTORES / AUTHORS: - Hofmann G; Balic M; Dandachi N; Resel M; Schippinger W; Regitnig P; Samonigg H; Bauernhofer T

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

RESUMEN / SUMMARY: - OBJECTIVES: To date, no reliable markers are available to predict response to or to assess prognosis after preoperative systemic chemotherapy (PST) in patients with locally advanced breast cancer. Previous studies demonstrated that elevated levels of soluble E-cadherin (sE-cadherin), a product of proteolytic cleavage of cell surface E-cadherin, are

associated with higher risk for metastatic disease and poor prognosis in various tumor types. We, therefore, hypothesized that serum sE-cadherin levels measured before PST may correlate with pathological response. DESIGN AND METHODS: In a retrospective analysis, sE-cadherin levels were measured in sera of 108 female patients with histologically proven breast cancer before initiation of PST by using a commercially available quantitative sandwich enzyme immunoassay technique. Patients received a median number of 4 (range 3-6) cycles of anthracycline-based chemotherapy. The median patient age was 51.5 (range 21-71) years. Tumor size was measured clinically and translated into the tumor-node-metastasis (TNM)-system before the start of chemotherapy. Histopathological response in surgically removed specimens was evaluated using a modified Sinn regression score. In univariate analyses the correlations between levels of sE-cadherin and pathological response to PST were calculated. RESULTS: The histopathological regression scores correlated significantly with tumor grading ($p=0.045$), clinical lymph node status before PST ($p=0.031$) and sE-cadherin levels ($p=0.039$). No correlation was seen between histopathological regression scores and hormone receptor and menopausal status as well as Her2-neu status. CONCLUSION: sE-cadherin may be a marker predicting response to PST for patients with breast cancer. Our findings warrant further evaluation of sE-cadherin in a prospective trial.

[169]

TÍTULO / TITLE: - Targeting prostate cancer cell lines with polo-like kinase 1 inhibitors as a single agent and in combination with histone deacetylase inhibitors.

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

REVISTA / JOURNAL: - FASEB J. 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [1096/fj.12-222893](#)

AUTORES / AUTHORS: - Wissing MD; Mendonca J; Kortenhorst MS; Kaelber NS; Gonzalez M; Kim E; Hammers H; van Diest PJ; Carducci MA; Kachhap SK

INSTITUCIÓN / INSTITUTION: - *Prostate Cancer Program of the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA;

RESUMEN / SUMMARY: - Combinations of anticancer therapies with high efficacy and low toxicities are highly sought after. Therefore, we studied the effect of polo-like kinase 1 (Plk1) inhibitors on prostate cancer cells as a single agent and in combination with histone deacetylase (HDAC) inhibitors valproic acid and vorinostat. IC50s of Plk1 inhibitors BI 2536 and BI 6727 were determined in prostate cancer cells by MTS assays. Morphological and molecular changes were assessed by immunoblotting, immunofluorescence, flow cytometry, real-time RT-PCR, and pull-down assays. Efficacy of combination therapy was assessed by MTS and clonogenic assays. IC50 values in DU145, LNCaP, and PC3 cells were 50, 75, and 175 nM, respectively, for BI 2536 and 2.5, 5, and

600 nM, respectively, for BI 6727. Human prostate fibroblasts and normal prostate epithelial cells were unaffected at these concentrations. While DU145 and LNCaP cells were solely arrested in mitosis on treatment, PC3 cells accumulated in G2 phase and mitosis, suggesting a weak spindle assembly checkpoint. Combining Plk1 inhibitors with HDAC inhibitors had synergistic antitumor effects in vitro. DMSO-treated prostate cancer cells were used as controls to study the effect of Plk1 and HDAC inhibition. Plk1 inhibitors decreased proliferation and clonogenic potential of prostate cancer cells. Hence, Plk1 may serve as an important molecular target for inhibiting prostate cancer. Combining HDAC inhibitors with BI 2536 or BI 6727 may be an effective treatment strategy against prostate cancer.-Wissing, M. D., Mendonca, J., Kortenhorst, M. S. Q., Kaelber, N. S., Gonzalez, M., Kim E., Hammers, H., van Diest, P. J., Carducci, M. A., Kachhap, S. K. Targeting prostate cancer cell lines with polo-like kinase 1 inhibitors as a single agent and in combination with histone deacetylase inhibitors.

[170]

TÍTULO / TITLE: - Identification of Sirtuin 3, a mitochondrial protein deacetylase, as a new contributor to tamoxifen resistance in breast cancer cells.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Jul 12. pii: S0006-2952(13)00422-X. doi: 10.1016/j.bcp.2013.06.032.

●● Enlace al texto completo (gratis o de pago) 1016/j.bcp.2013.06.032

AUTORES / AUTHORS: - Zhang L; Ren X; Cheng Y; Huber-Keener K; Liu X; Zhang Y; Yuan YS; Yang JW; Liu CG; Yang JM

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and The Penn State Hershey Cancer Institute, The Pennsylvania State University College of Medicine and Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033, United States.

RESUMEN / SUMMARY: - The current study reports a previously unappreciated role of Sirtuin 3 (SIRT3), a mitochondrial protein deacetylase, in altering sensitivity of breast cancer cells to tamoxifen (Tam), a commonly used anti-estrogen agent. We showed that SIRT3 was significantly up-regulated at both mRNA and protein levels in the Tam-resistance human breast cancer cell line MTR-3, which was derived from MCF-7 line by continuous selective culture in the presence of 1µM of Tam for two years. We further demonstrated that SIRT3 was rapidly up-regulated in the sensitive MCF-7 cells following exposure to Tam. Transfection of MCF-7 cells with a SIRT3 expression plasmid decreased cellular sensitivity to Tam and blocked the Tam-induced apoptosis. Furthermore, silencing of SIRT3 expression in MTR-3 cells sensitized the resistant cells to Tam and enhanced apoptotic cell death. MTR-3 cells with silencing of SIRT3 expression showed increases in the mitochondrial content of ERbeta, ROS level and apoptosis. These results not only uncovered a new role

for SIRT3 in cancer but also identified this mitochondrial protein deacetylase as a previously unrecognized factor that participates in regulation of Tam sensitivity in breast cancer cells. Thus, SIRT3 might be considered as a potential target for overcoming Tam resistance in treatment of breast cancer.

[171]

TÍTULO / TITLE: - Extranodal Marginal Zone Lymphoma Arising in a Chronic Myelogenous Leukemia Patient on Long-Term Tyrosine Kinase Inhibitors.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jun 7.

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

3109/10428194.2013.811581

AUTORES / AUTHORS: - Xu X; Hassan A

[172]

TÍTULO / TITLE: - Use of tyrosine kinase inhibitors in a patient with Brugada syndrome and chronic myeloid leukemia.

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

REVISTA / JOURNAL: - Int J Hematol. 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [1007/s12185-013-1395-](http://1007/s12185-013-1395-8)

[8](#)

AUTORES / AUTHORS: - Sgherza N; Russo Rossi AV; Colonna P; Carluccio P; Delia M; Specchia G

INSTITUCIÓN / INSTITUTION: - U.O. Ematologia con Trapianto, D.E.T.O., Università degli Studi di Bari "Aldo Moro", Piazza Giulio Cesare 11, 70124, Bari, Italy, nicolasgherza@libero.it.

RESUMEN / SUMMARY: - The treatment and prognosis of chronic myeloid leukemia have dramatically changed since the introduction of tyrosine kinase inhibitors, but although several clinical trials have examined their safety with respect to heart function, no data are yet available about the use of these drugs in patients with Brugada syndrome. We report a case of Brugada syndrome diagnosed during tyrosine kinase inhibitor therapy in a 69-year-old Caucasian male with meningioma and chronic myeloid leukemia. This case report highlights the importance of an integrated approach among hematologists and cardiologists to ensure appropriate treatment with tyrosine kinase inhibitors in patients affected by chronic myeloid leukemia who also suffer from Brugada syndrome.

[173]

TÍTULO / TITLE: - A dose-escalation study of recombinant human interleukin-18 in combination with rituximab in patients with non-hodgkin lymphoma.

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

REVISTA / JOURNAL: - J Immunother. 2013 Jul-Aug;36(6):331-41. doi: 10.1097/CJI.0b013e31829d7e2e.

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

[1097/CJI.0b013e31829d7e2e](#)

AUTORES / AUTHORS: - Robertson MJ; Kline J; Struemper H; Koch KM; Bauman JW; Gardner OS; Murray SC; Germaschewski F; Weisenbach J; Jonak Z; Toso JF

INSTITUCIÓN / INSTITUTION: - *Department of Medicine, Division of Hematology/Oncology, Lymphoma Program, Indiana University School of Medicine, Indianapolis, IN daggerSection of Hematology/Oncology, University of Chicago, Chicago, IL double daggerGlaxoSmithKline Inc., Research Triangle Park, NC.

RESUMEN / SUMMARY: - Interleukin-18 (IL-18) is an immunostimulatory cytokine with antitumor activity in preclinical models. Rituximab is a CD20 monoclonal antibody with activity against human B-cell lymphomas. A phase I study of recombinant human (rh) IL-18 given with rituximab was performed in patients with CD20 lymphoma. Cohorts of 3-4 patients were given infusions of rituximab (375 mg/m²) weekly for 4 weeks with escalating doses of rhIL-18 as a 2-hour intravenous infusion weekly for 12 consecutive weeks. Toxicities were graded using standard criteria. Blood samples were obtained for safety, pharmacokinetic, and pharmacodynamic studies. Nineteen patients with CD20 B-cell non-Hodgkin lymphoma were given rituximab in combination with rhIL-18 at doses of 1, 3, 10, 20, 30, and 100 µg/kg. Common side effects included chills, fever, headache, and nausea. Common laboratory abnormalities included transient, asymptomatic lymphopenia, hyperglycemia, anemia, hypoalbuminemia, and bilirubin and liver enzyme elevations. No dose-limiting toxicities were observed. Biologic effects of rhIL-18 included transient lymphopenia and increased expression of activation antigens on lymphocytes. Increases in serum concentrations of IFN-gamma, GM-CSF, and chemokines were observed after dosing. Objective tumor responses were seen in 5 patients, including 2 complete and 3 partial responses. rhIL-18 can be given in biologically active doses by weekly infusions in combination with rituximab to patients with lymphoma. A maximum tolerated dose of rhIL-18 plus rituximab was not determined. Further studies of rhIL-18 and CD20 monoclonal antibodies in B-cell malignancies are warranted.

[174]

TÍTULO / TITLE: - Scheduling of paclitaxel and gefitinib to inhibit repopulation for optimal treatment of human cancer cells and xenografts that overexpress the epidermal growth factor receptor.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Jul 14.

- Enlace al texto completo (gratis o de pago) [1007/s00280-013-2229-](https://doi.org/10.1007/s00280-013-2229-3)

3

AUTORES / AUTHORS: - Fung AS; Yu M; Ye QJ; Tannock IF

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, 610 University Avenue, Toronto, ON, M5G 2M9, Canada.

RESUMEN / SUMMARY: - **PURPOSE:** In clinical studies, evaluating the combination of chemotherapy and the epidermal growth factor receptor (EGFR) inhibitor gefitinib, treatments were administered concurrently, despite it being counter-intuitive to give a cytostatic agent concurrent with cycle-active chemotherapy. One strategy to enhance efficacy might be to give the agents sequentially, thus allowing selective inhibition of repopulation of cancer cells between doses of chemotherapy. Here, we evaluate the hypothesis that sequential administration might allow inhibition of repopulation by gefitinib, with tumor cells re-entering cycle to allow sensitivity to subsequent chemotherapy. **METHODS:** Sequential and concurrent administration of paclitaxel and gefitinib were studied in vitro and in xenografts using EGFR over-expressing, EGFR-mutant, and EGFR wild-type human cancer cell lines. We evaluated cell cycle distribution and repopulation during treatment. **RESULTS:** The sequential use of gefitinib and paclitaxel to treat EGFR over-expressing A431 cells in vitro decreased repopulation compared to chemotherapy alone, and there was greater cell kill compared to concurrent treatment. In contrast, combined treatment led to greater growth delay than use of gefitinib alone for concurrent but not for sequential treatment of mice bearing A431 xenografts; concurrent treatment had greater effects to reduce functional vasculature in the tumors. Conversely, sequential treatment led to greater growth delay than concurrent treatment of EGFR-mutant HCC-827 xenografts that are sensitive to lower doses of gefitinib. **CONCLUSIONS:** These studies highlight the importance of considering effects on the cell cycle, and on the solid tumor microenvironment, including tumor vasculature, when scheduling cytostatic and cytotoxic agents in combination.

[175]

TÍTULO / TITLE: - Role of Goserelin in Combination with Endocrine Therapy for the Treatment of Advanced Breast Cancer in Premenopausal Women Positive for Hormone Receptor: A Retrospective Matched Case-Control Study.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 Jun 27.

- Enlace al texto completo (gratis o de pago) [1089/cbr.2012.1436](https://doi.org/10.1089/cbr.2012.1436)

AUTORES / AUTHORS: - Wu S; Li Q; Zhu Y; Sun J; Li F; Lin H; Guan X; He Z

INSTITUCIÓN / INSTITUTION: - 1 Department of Radiation Oncology, Xiamen Cancer Center, The First Affiliated Hospital of Xiamen University, Xiamen, People's Republic of China.

RESUMEN / SUMMARY: - Abstract Objective: This research was to investigate the role of goserelin in combination with endocrine therapy for the treatment of advanced breast cancer in premenopausal women positive for hormone receptors. Methods: We retrospectively analyzed 40 patients as the treatment group with advanced breast cancer who, were positive for hormone receptors, received goserelin in combination with endocrine therapy and 40 patients as the control group received endocrine therapy alone, matched for age, gender, receptor status, and tumor stage. Results: The median period of follow-up was 38.9 months. The response status at 6 months, the overall clinical benefit rate was 87.5% and 70.0% in the treatment group and control group, respectively. The mean progression-free survival (PFS) in the treatment group and control group was 27.9 and 16.9 months, respectively. The 1-, 2-, and 3-year PFS rates were 87.5%, 66.2%, and 49.7%, respectively, in the treatment group and 59.2%, 38.8%, and 35.3%, respectively, in the control group (p=0.076). The 1-, 2-, and 3-year overall survival (OS) rates were 100%, 87.2%, and 76.6%, respectively, in the treatment group and 90.0%, 74.2%, and 55.8%, respectively, in the control group (p=0.048). For the treatment group with age <40 years, PFS (p=0.036) and OS (p=0.014) were significantly longer than the control group, but it was no effect on the prognosis with the patients aged \geq 40 years. Continued use of goserelin after disease progress again in the median survival time was significantly longer than nonusers (28.2 months vs. 7.0 months), and there is the potential benefit of OS (p=0.070). Conclusions: For premenopausal hormone receptor-positive advanced breast cancer, goserelin-combined endocrine therapy can be used for those <40 years, the standard endocrine treatment for patients, we recommend continued use of goserelin for patients with disease progress again.

[176]

TÍTULO / TITLE: - Mutation of the colony-stimulating factor-3 receptor gene is a rare event with poor prognosis in chronic myelomonocytic leukemia.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jun 18. doi: 10.1038/leu.2013.182.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.182](#)

AUTORES / AUTHORS: - Kosmider O; Itzykson R; Chesnais V; Lasho T; Laborde R; Knudson R; Gauthier A; Merlevede J; Ades L; Morabito M; Fontenay M; Tefferi A; Droin N; Solary E

INSTITUCIÓN / INSTITUTION: - [1] Institut Cochin, Paris, France [2] Universite Paris Descartes, Paris, France [3] Assistance Publique-Hopitaux de Paris, Hopital Cochin, Paris, France.

[177]

TÍTULO / TITLE: - The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Jul 25. pii: S0169-5002(13)00269-9. doi: 10.1016/j.lungcan.2013.06.012.

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

[1016/j.lungcan.2013.06.012](#)

AUTORES / AUTHORS: - Tsuta K; Kawago M; Inoue E; Yoshida A; Takahashi F; Sakurai H; Watanabe SI; Takeuchi M; Furuta K; Asamura H; Tsuda H

INSTITUCIÓN / INSTITUTION: - Division of Pathology and Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan. Electronic address: ktsuta@ncc.go.jp.

RESUMEN / SUMMARY: - BACKGROUND: The present study aimed to determine the ability of the revised International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification of lung adenocarcinoma to predict patient survivals and driver gene alterations. PATIENTS AND METHODS: A reclassification of 904 surgically resected adenocarcinomas was performed. The results were statistically analyzed to examine the correlation between the classification and overall survival (OS) using Cox regression analyses, and integrated discrimination improvement (IDI) analyses. RESULTS: The 5-year OS rates for adenocarcinomas in situ (AIS) or minimally invasive adenocarcinoma (MIA) were 98%. Five-year OS rates of Lepidic-, acinar-, papillary-, micropapillary-, and solid-predominant adenocarcinomas was 93%, 67%, 74%, 62%, and 58%, respectively. The IDI estimates revealed that classification of ADC into the 7 subgroups had a higher estimated (0.0175) than did the combined histological grouping (AIS+MIA, lepidic+acinar+papillary, micropapillary+solid+others) (0.0111). Epidermal growth factor receptor mutations, KRAS gene mutations, and anaplastic lymphoma kinase gene alterations were statistically prevalent in papillary-predominant (P=0.00001), invasive mucinous (P=0.00001), and micropapillary- and acinar-predominant (P=0.00001) adenocarcinomas, respectively. CONCLUSIONS: The new classification reflects disease prognosis, and was also associated with driver gene alterations.

[178]

TÍTULO / TITLE: - Hypermethylation reduces expression of tumor-suppressor PLZF and regulates proliferation and apoptosis in non-small-cell lung cancers.

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

REVISTA / JOURNAL: - FASEB J. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1096/fj.13-229070](#)

AUTORES / AUTHORS: - Wang X; Wang L; Guo S; Bao Y; Ma Y; Yan F; Xu K; Xu Z; Jin L; Lu D; Xu J; Wang JC

INSTITUCIÓN / INSTITUTION: - *State Key Laboratory of Genetic Engineering and daggerMinistry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China;

RESUMEN / SUMMARY: - Deregulation of promyelocytic leukemia zinc finger protein (PLZF), a tumor suppressor gene, was reported in different types of solid tumors. This study for the first time explored the reduced expression of PLZF and its effects in non-small-cell lung cancer (NSCLC) carcinogenesis. PLZF was found to be down-regulated by 62.8% in 87.1% of 154 paired NSCLC samples by quantitative real-time PCR, and its expression was found to be associated with the sex of the patient ($P=0.02$). Further analysis showed that down-regulation of PLZF in 35.6% NSCLC samples (31 out of 87) was triggered by hypermethylation in the promoter region. This was validated by demethylation analysis using the A549 cell line. Dual-luciferase reporter assay indicated that CTCF binding to the promoter region could activate PLZF transcription. Overexpression of PLZF in both A549 and LTEP lung cancer cell lines was found to inhibit proliferation and increase apoptosis. Therefore, reduced expression of PLZF was found to be common in NSCLC. PLZF down-regulation was partially correlated with hypermethylation in the promoter region. Decreased levels of PLZF expression may contribute to the pathogenesis of NSCLC by promoting cell survival. Therefore, the restoration of PLZF expression may serve as a new strategy for NSCLC therapy.-Wang, X., Wang, L., Guo, S., Bao, Y., Ma, Y., Yan, F., Xu, K., Xu, Z., Jin, L., Lu, D., Xu, J., Wang, J.-C. Hypermethylation reduces expression of tumor-suppressor PLZF and regulates proliferation and apoptosis in non-small-cell lung cancers.

[179]

TÍTULO / TITLE: - Ovarian cancer G protein-coupled receptor 1 is involved in acid-induced apoptosis of endplate chondrocytes in intervertebral discs.

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

REVISTA / JOURNAL: - J Bone Miner Res. 2013 Jul 2. doi: 10.1002/jbmr.2030.

●● Enlace al texto completo (gratis o de pago) [1002/jbmr.2030](#)

AUTORES / AUTHORS: - Yuan FL; Wang HR; Yuan W; Zhao MD; Cao L; Duan PG; Jiang YQ; Li XL; Dong J

INSTITUCIÓN / INSTITUTION: - Department of Orthopedic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - Ovarian cancer G protein-coupled receptor 1 (OGR1) has been shown to be a receptor for protons. We investigated the role of proton-sensing G protein-coupled receptors in the apoptosis of endplate chondrocytes induced by extracellular acid. The expression of proton-sensing G protein-coupled receptors was examined in rat lumbar endplate chondrocytes. Knockdown of OGR1 was achieved by transfecting chondrocytes with specific short hairpin RNA (shRNA) for OGR1. Apoptotic changes were evaluated by DNA fragmentation ELISA, electron microscopy, and flow cytometry.

Intracellular calcium ($[Ca^{2+}]_i$) was analyzed with laser scanning confocal microscopy. The mechanism of OGR1 in acid-induced apoptosis of endplate chondrocytes was also investigated. We found that OGR1 was predominantly expressed in rat endplate chondrocytes, and its expression was highly upregulated in response to acidosis. Knocking down OGR1 with shRNAs effectively attenuated acid-induced apoptosis of endplate chondrocytes and increased $[Ca^{2+}]_i$. Blocking OGR1-mediated $[Ca^{2+}]_i$ elevation inhibited acid-induced calcium-sensitive proteases such as calpain and calcineurin, and also inhibited the activation of Bid, Bax, and Caspase 3 and cleavage of poly (ADP-ribose) polymerase (PARP). OGR1-mediated $[Ca^{2+}]_i$ elevation has a crucial role in apoptosis of endplate chondrocytes by regulating activation of calcium-sensitive proteases and their downstream signaling.

[180]

TÍTULO / TITLE: - Prospective study assessing hypoxia-related proteins as markers for the outcome of treatment with sunitinib in advanced clear-cell renal cell carcinoma.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Jun 20.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt219](#)

AUTORES / AUTHORS: - Garcia-Donas J; Leandro-Garcia LJ; Gonzalez Del Alba A; Morente M; Alemany I; Esteban E; Arranz JA; Climent MA; Gallardo E; Castellano DE; Bellmunt J; Mellado B; Puente J; Moreno F; Font A; Hernando S; Robledo M; Rodriguez-Antona C

INSTITUCIÓN / INSTITUTION: - Genitourinary and Gynecological Tumors and Rare Cancer Programme, Centro Integral Oncologico Clara Campal, Madrid.

RESUMEN / SUMMARY: - BACKGROUND: Previous studies suggest that expression of hypoxia markers may be associated with response to antiangiogenic drugs. Thus, we aimed to identify predictors of sunitinib outcome in clear-cell renal cell carcinoma (ccRCC). PATIENTS AND METHODS: The expression of eight key proteins related to hypoxia (CAIX, HIF1A, HIF2A, VEGFA, VEGFR1, VEGFR2, VEGFR3 and PDGFRB) and P-glycoprotein were assessed by immunohistochemistry in 67 primary ccRCC samples from prospectively recruited patients treated with first-line sunitinib. The proteins expression, VHL inactivation and EGLN3 mRNA content were compared with the patients' response to sunitinib. RESULTS: High expression of HIF2A and PDGFRB was associated with better sunitinib RECIST objective response ($P = 0.024$ and $P = 0.026$; respectively) and increased VEGFR3 expression was associated with longer progression-free survival ($P = 0.012$). VEGFR3 overexpression showed a negative correlation with VEGFR3 polymorphism rs307826 ($P = 0.002$), a sunitinib resistance predictor. With respect to overall survival (OS), high VEGFA was associated with short ($P = 0.009$) and HIF2A with long ($P = 0.048$) survival times. High EGLN3 mRNA content was

associated with shorter OS ($P = 0.023$). CONCLUSIONS: We found an association between several proteins involved in hypoxia and sunitinib efficacy. In addition, low VEGFR3 expression was associated with worse outcome and with VEGFR3 rs307826 variant allele, reinforcing VEGFR3 as a marker of sunitinib resistance.

[181]

TÍTULO / TITLE: - Circulating microRNAs predict biochemical recurrence in prostate cancer patients.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 6;109(3):641-50. doi: 10.1038/bjc.2013.369. Epub 2013 Jul 11.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.369](#)

AUTORES / AUTHORS: - Selth LA; Townley SL; Bert AG; Stricker PD; Sutherland PD; Horvath LG; Goodall GJ; Butler LM; Tilley WD

INSTITUCIÓN / INSTITUTION: - Dame Roma Mitchell Cancer Research Laboratories, Adelaide Prostate Cancer Research Centre, University of Adelaide and Hanson Institute, PO Box 14, Rundle Mall, Adelaide, South Australia 5000, Australia.

RESUMEN / SUMMARY: - Background:Circulating microRNAs (miRNAs) are emerging as promising biomarkers for prostate cancer. Here, we investigated the potential of these molecules to assist in prognosis and treatment decision-making.Methods:MicroRNAs in the serum of patients who had experienced rapid biochemical recurrence (BCR) ($n=8$) or no recurrence ($n=8$) following radical prostatectomy (RP) were profiled using high-throughput qRT-PCR. Recurrence-associated miRNAs were subsequently quantitated by qRT-PCR in a validation cohort comprised of 70 patients with Gleason 7 cancers treated by RP, 31 of whom had undergone disease progression following surgery. The expression of recurrence-associated miRNAs was also examined in tumour tissue cohorts.Results:Three miRNAs - miR-141, miR-146b-3p and miR-194 - were elevated in patients who subsequently experienced BCR in the screening study. MiR-146b-3p and miR-194 were also associated with disease progression in the validation cohort, as determined by log-rank tests and Cox proportional hazards regression. Multivariate analysis revealed that miR-146b-3p possessed prognostic information beyond standard clinicopathological parameters. Analysis of tissue cohorts revealed that miR-194 was robustly expressed in the prostate, elevated in metastases, and its expression in primary tumours was associated with a poor prognosis.Conclusion:Our study suggests that circulating miRNAs, measured at the time of RP, could be combined with current prognostic tools to predict future disease progression in men with intermediate risk prostate cancers.

[182]

TÍTULO / TITLE: - Melatonin induces apoptosis through a caspase-dependent but reactive oxygen species-independent mechanism in human leukemia Molt-3 cells.

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

REVISTA / JOURNAL: - J Pineal Res. 2013 Sep;55(2):195-206. doi: 10.1111/jpi.12062. Epub 2013 Jun 1.

●● [Enlace al texto completo \(gratis o de pago\) 1111/jpi.12062](#)

AUTORES / AUTHORS: - Perdomo J; Cabrera J; Estevez F; Loro J; Reiter RJ; Quintana J

INSTITUCIÓN / INSTITUTION: - Departamento de Bioquímica y Biología Molecular, Fisiología, Genética e Inmunología, Facultad de Ciencias de la Salud, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, España.

RESUMEN / SUMMARY: - Melatonin is a naturally occurring indoleamine synthesized in the pineal gland that exhibits an extensive repertoire of biological activities. An increasing number of studies indicate that melatonin protects normal cells, while it reducing cancer cell proliferation. In this study, we investigated the effect of melatonin on the growth of the human leukemia cells and found that it efficiently reduced the number of cells in a concentration- and time-dependent manner. Thus, incubation with the indoleamine increased the percentage of cells with a hypodiploid DNA content, augmented the number of annexin V-positive cells, and also provoked ultrastructural changes that are features of apoptotic cell death. Evaluation of caspases revealed that caspase-3, caspase-6, caspase-7, and caspase-9, but not caspase-8 and caspase-2, were quickly activated (3-6 hr). The increase in the activity of these proteases was associated with up-regulation of the pro-apoptotic factor Bax and also with the release of cytochrome c from mitochondria. Pretreatment of the cells with the general caspase inhibitor z-VAD-fmk, reduced melatonin-induced apoptosis, but it did not block cell death suggesting that melatonin activates an alternative cell death modality in the absence of caspase activity. Thus, the activation of caspases was preceded by a fast (<30 min) increase in reactive oxygen species (ROS). Rotenone and antimycin A reduced the levels of ROS stimulated by melatonin, indicating that the complex I and the complex III of the mitochondrial electron transport chain are important sources of these chemical species. However, the role of ROS in melatonin-induced cell death remains elusive because anti-oxidants that were shown to decrease ROS levels (glutathione, N-acetyl-l-cysteine and Trolox) were unable to abrogate melatonin-induced cell death.

[183]

TÍTULO / TITLE: - Enhancement of (-)-epigallocatechin-3-gallate and theaflavin-3-3'-digallate induced apoptosis by ascorbic acid in human lung adenocarcinoma SPC-A-1 cells and esophageal carcinoma Eca-109 cells via MAPK pathways.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 26. pii: S0006-291X(13)01240-0. doi: 10.1016/j.bbrc.2013.07.078.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.07.078](#)

AUTORES / AUTHORS: - Gao Y; Li W; Jia L; Li B; Chen YC; Tu Y

INSTITUCIÓN / INSTITUTION: - Department of Tea Science, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, China.

RESUMEN / SUMMARY: - Tea polyphenols (-)-epigallocatechin-3-gallate (EGCG) and theaflavin-3-3'-digallate (TF3) are two prospective compounds in cancer prevention and treatment. Ascorbic acid (Vc) is essential to a healthy diet as well as being a highly effective antioxidant. In this work, the effects of the combination of EGCG or TF3 with Vc on the apoptosis and caspases-3/9 activities in human lung adenocarcinoma SPC-A-1 cells and esophageal carcinoma Eca-109 cells were determined. Furthermore, the role of mitogen-activated protein kinases (MAPK) pathways in the apoptosis induced by TF3 or EGCG together with Vc were studied using three MAPK inhibitors (ERK inhibitor PD98059, JNK inhibitor SP600125 and p38 inhibitor SB203580). Our results showed that Vc could enhance the EGCG and TF3 induced apoptosis in SPC-A-1 and Eca-109 cells, and this effect involved the activation of caspase-3 and 9. EGCG, TF3 and Vc could activate MAPK pathways respectively, and each compound activated different MAPK subfamilies in different cells. This may explain the enhancement of EGCG and TF3 induced apoptosis by Vc in SPC-A-1 Eca-109 cells, and will ultimately aid the design of more effective anti-cancer treatments.

[184]

TÍTULO / TITLE: - A leukotriene B4 receptor-2 is associated with paclitaxel resistance in MCF-7/DOX breast cancer cells.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 23;109(2):351-9. doi: 10.1038/bjc.2013.333. Epub 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.333](#)

AUTORES / AUTHORS: - Kim H; Park GS; Lee JE; Kim JH

INSTITUCIÓN / INSTITUTION: - School of Life Sciences and Biotechnology, Korea University, 5-1 Anam-dong, Sungbuk-gu, Seoul, 136-701, Korea.

RESUMEN / SUMMARY: - Background: Breast cancer is the most common malignancy in women. Although chemotherapeutic agents, such as paclitaxel, are effective treatments for the majority of breast cancer patients, recurrence is frequent and often leads to death. Thus, there is an urgent need to identify novel therapeutic targets that sensitise tumour cells to existing chemotherapy

agents. Methods: The levels of leukotriene B4 receptor-2 (BLT2) in multidrug-resistant MCF-7/DOX cells were determined using quantitative PCR and FACS analysis. The potential role of BLT2 in the paclitaxel resistance of MCF-7/DOX cells was assessed using a pharmacological inhibitor and small interfering RNA knockdown, and the BLT2-associated resistance mechanism was assessed. Results: The expression levels of BLT2 were markedly upregulated in MCF-7/DOX cells. The inhibition of BLT2 by pre-treatment with LY255283 or siBLT2 knockdown significantly sensitised MCF-7/DOX cells to paclitaxel and induced significant levels of apoptotic death, suggesting that BLT2 mediates paclitaxel resistance. We also demonstrated that BLT2-induced paclitaxel resistance was associated with the upregulation of P-glycoprotein. Finally, co-treatment with a BLT2 inhibitor and paclitaxel markedly reduced tumour growth in an MCF-7/DOX in vivo model. Conclusion: Together, our results demonstrate that BLT2 is a novel therapeutic target that sensitises drug-resistant breast cancer cells to paclitaxel.

[185]

TÍTULO / TITLE: - The Src Homology 3 Domain-containing Guanine Nucleotide Exchange Factor Is Overexpressed in High-grade Gliomas and Promotes Tumor Necrosis Factor-like Weak Inducer of Apoptosis-Fibroblast Growth Factor-inducible 14-induced Cell Migration and Invasion via Tumor Necrosis Factor Receptor-associated Factor 2.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jul 26;288(30):21887-97. doi: 10.1074/jbc.M113.468686. Epub 2013 Jun 17.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.468686](#)

AUTORES / AUTHORS: - Fortin Ensign SP; Mathews IT; Eschbacher JM; Loftus JC; Symons MH; Tran NL

INSTITUCIÓN / INSTITUTION: - From the Cancer and Cell Biology Division, The Translational Genomics Research Institute, Phoenix, Arizona 85004.

RESUMEN / SUMMARY: - Glioblastoma (GB) is the highest grade of primary adult brain tumors, characterized by a poorly defined and highly invasive cell population. Importantly, these invading cells are attributed with having a decreased sensitivity to radiation and chemotherapy. TNF-like weak inducer of apoptosis (TWEAK)-Fn14 ligand-receptor signaling is one mechanism in GB that promotes cell invasiveness and survival and is dependent upon the activity of multiple Rho GTPases, including Rac1. Here we report that Src homology 3 domain-containing guanine nucleotide exchange factor (SGEF), a RhoG-specific guanine nucleotide exchange factor, is overexpressed in GB tumors and promotes TWEAK-Fn14-mediated glioma invasion. Importantly, levels of SGEF expression in GB tumors inversely correlate with patient survival. SGEF mRNA expression is increased in GB cells at the invasive rim relative to those in the tumor core, and knockdown of SGEF expression by shRNA decreases

glioma cell migration in vitro and invasion ex vivo. Furthermore, we showed that, upon TWEAK stimulation, SGEF is recruited to the Fn14 cytoplasmic tail via TRAF2. Mutation of the Fn14-TRAF domain site or depletion of TNF receptor-associated factor 2 (TRAF2) expression by siRNA oligonucleotides blocked SGEF recruitment to Fn14 and inhibited SGEF activity and subsequent GB cell migration. We also showed that knockdown of either SGEF or RhoG diminished TWEAK activation of Rac1 and subsequent lamellipodia formation. Together, these results indicate that SGEF-RhoG is an important downstream regulator of TWEAK-Fn14-driven GB cell migration and invasion.

PTPTPTP - Journal Article

[186]

TÍTULO / TITLE: - Linking genomic lesions with minimal residual disease improves prognostic stratification in children with T-cell acute lymphoblastic leukaemia.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Aug;37(8):928-35. doi: 10.1016/j.leukres.2013.04.005. Epub 2013 Jun 2.

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

[1016/j.leukres.2013.04.005](#)

AUTORES / AUTHORS: - La Starza R; Lettieri A; Pierini V; Nofrini V; Gorello P; Songia S; Crescenzi B; Te Kronnie G; Giordan M; Leszl A; Valsecchi MG; Aversa F; Basso G; Biondi A; Conter V; Cazzaniga G; Mecucci C

INSTITUCIÓN / INSTITUTION: - Hematology Unit, University of Perugia, Polo Unico S.M. Misericordia, Perugia, Italy.

RESUMEN / SUMMARY: - Multiple lesions in genes that are involved in cell cycle control, proliferation, survival and differentiation underlie T-cell acute lymphoblastic leukaemia (T-ALL). We translated these biological insights into clinical practice to improve diagnostic work-ups and patient management. Combined interphase fluorescence in situ hybridization (CI-FISH), single nucleotide polymorphism (SNP), and gene expression profiles (GEP) were applied in 51 children with T-ALL who were stratified according to minimal residual disease (MRD) risk categories (AIEOP-BFM ALL2000). CI-FISH identified type A abnormalities in 90% of patients. Distribution of each was in line with the estimated incidence in childhood T-ALL: 37.5% TAL/LMO, 22.5% HOXA, 20% TLX3, 7.5% TLX1, and 2.5% NKX2-1. GEP predictions concurred. SNP detected type B abnormalities in all cases, thus linking type A and B lesions. This approach provided an accurate, comprehensive genomic diagnosis and a complementary GEP-based classification of T-ALL in children. Dissecting primary and secondary lesions within MRD categories could improve prognostic criteria for the majority of patients and be a step towards personalized diagnosis.

[187]

TÍTULO / TITLE: - Curcumin enhances TRAIL-induced apoptosis of breast cancer cells by regulating apoptosis-related proteins.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1752-](#)

[1](#)

AUTORES / AUTHORS: - Park S; Cho DH; Andera L; Suh N; Kim I

INSTITUCIÓN / INSTITUTION: - Asan Institute for Life Sciences, Asan Medical Center, Seoul, 138-736, Republic of Korea.

RESUMEN / SUMMARY: - The TNF-related apoptosis inducing ligand (TRAIL) has promising anti-cancer therapeutic activity, although significant percentage of primary tumors resistant to TRAIL-induced apoptosis remains an obstacle to the extensive use of TRAIL-based mono-therapies. Natural compound curcumin could potentially sensitize resistant cancer cells to TRAIL. We found that the combination of TRAIL with curcumin can synergistically induce apoptosis in three TRAIL-resistant breast cancer cell lines. The mechanism behind this synergistic cell death was investigated by examining an effect of curcumin on the expression and activation of TRAIL-associated cell death proteins.

Immunoblotting, RNA interference, and use of chemical inhibitors of TRAIL-activate signaling revealed differential effects of curcumin on the expression of Mcl-1 and activities of ERK and Akt. Curcumin-induced production of reactive oxygen species did not affect total expression of DR5 but it enhanced mobilization of DR5 to the plasma membrane. In these breast cancer cells curcumin also induced downregulation of IAP proteins. Taken together, our data suggest that a combination of TRAIL and curcumin is a potentially promising treatment for breast cancer, although the specific mechanisms involved in this sensitization could differ even among breast cancer cells of different origins.

[188]

TÍTULO / TITLE: - A phase I dose escalation study to determine the optimal biological dose of irosustat, an oral steroid sulfatase inhibitor, in postmenopausal women with estrogen receptor-positive breast cancer.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2597-](#)

[8](#)

AUTORES / AUTHORS: - Coombes RC; Cardoso F; Isambert N; Lesimple T; Soulie P; Péraire C; Fohanno V; Kornowski A; Ali T; Schmid P

INSTITUCIÓN / INSTITUTION: - Department of Cancer and Surgery, Faculty of Medicine, ICTEM, Imperial College London, Room 145, Du Cane Road, London, W12 0NN, UK, c.coombes@imperial.ac.uk.

RESUMEN / SUMMARY: - Steroid sulfatase (STS) inhibition may have a therapeutic role in suppression of endocrine-responsive breast cancer. This study aimed to determine the optimal biological dose and recommended dose (RD) of the STS inhibitor irosustat. A three-part, open-label, multicenter, dose escalation study of irosustat in estrogen receptor-positive breast cancer patients involved administration of a single dose of irosustat with a 7-day observation period; followed by a daily oral dose of irosustat for 28 days; and an extension phase, in which the daily oral dose of irosustat was continued at the discretion of the investigator and as long as the patient was benefitting from the treatment. Five doses of irosustat were tested (1, 5, 20, 40, and 80 mg) in 50 patients. After 28 days of daily administration of irosustat, all the evaluated patients in the 5, 20, 40, and 80 mg cohorts achieved $\geq 95\%$ STS inhibition in peripheral blood mononuclear cells and corresponding endocrine suppression. The maximum tolerated dose was not reached, and the 40 mg dose was established as the RD. The median time to disease progression in the 40 mg cohort was 11.2 weeks. Disease stabilization was achieved in 10 % of patients potentially indicative of drug activity. Dry skin was the most frequent adverse event. The RD of irosustat is 40 mg. Disease stabilization occurred in 10 % of this heavily pretreated patient population. A larger study is required to define an accurate response rate to irosustat as a single agent and whether co-administration with an aromatase inhibitor is needed.

[189]

TÍTULO / TITLE: - Isorhamnetin inhibits proliferation and invasion and induces apoptosis through the modulation of peroxisome proliferator-activated receptor gamma activation pathway in gastric cancer.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jun 28;288(26):18777. doi: 10.1074/jbc.A112.388702.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.A112.388702](#)

AUTORES / AUTHORS: - Ramachandran L; Manu KA; Shanmugam MK; Li F; Siveen KS; Vali S; Kapoor S; Abbasi T; Surana R; Smoot DT; Ashktorab H; Tan P; Ahn KS; Yap CW; Kumar AP; Sethi G

[190]

TÍTULO / TITLE: - Immunohistochemical expression of telomerase in patients with non-small cell lung cancer: prediction of metastasis and prognostic significance.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2643-50.

AUTORES / AUTHORS: - Aras G; Kanmaz D; Urer N; Purisa S; Kadakal F; Yenturk E; Tuncay E

INSTITUCIÓN / INSTITUTION: - Department of Chest Disease, Yedikule Chest Disease and Surgery Education and Research Hospital, Istanbul, Turkey. gulfidanaras@yahoo.com

RESUMEN / SUMMARY: - AIM: To detect telomerase reverse transcriptase (TERT) expression in tissue and metastatic and non-metastatic lymph node samples from patients with non-small cell lung cancer; to evaluate whether TERT expression is correlated with pathological and clinical features, and/or patient survival times; to determine differences between TERT expression in metastatic and non-metastatic lymph nodes. PATIENTS AND METHODS: Tumor tissue samples from 17 patients with squamous cell lung cancer and 11 patients with adenocarcinoma diagnosed between 2003 and 2004 were included in this study. All patients were diagnosed at our hospital and had samples stored in the pathology archive. Additionally, dissected lymph node samples, with and without metastases, were studied. Telomerase Gene Tex, Inc, Irvine, CA USA (TERT (2C4) antibody), Universal Kit (Lab Vision, Newmarket, UK) were used for immunohistochemical staining. Statistical analyses were performed using SPSS 17.0 statistical software. RESULTS: TERT was positive in 18/28 of the samples, regardless of the histological tumor type. There was no significant correlation between TERT expression in lymph nodes with metastasis and clinical stage, histological type, tumor differentiation, or survival time. CONCLUSION: TERT expression may be used as a target for therapy. It may also be helpful in predicting metastasis but not in predicting survival time.

[191]

TÍTULO / TITLE: - Survivin Inhibitor YM-155 Sensitizes Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand-Resistant Glioma Cells to Apoptosis through Mcl-1 Downregulation and by Engaging the Mitochondrial Death Pathway.

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

REVISTA / JOURNAL: - J Pharmacol Exp Ther. 2013 Aug;346(2):201-10. doi: 10.1124/jpet.113.204743. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) 1124/jpet.113.204743

AUTORES / AUTHORS: - Premkumar DR; Jane EP; Foster KA; Pollack IF

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Children's Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224. ian.pollack@chp.edu.

RESUMEN / SUMMARY: - Induction of apoptosis by the death ligand tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising antitumor therapy. However, not all tumor cells are sensitive to TRAIL, highlighting the need for strategies to overcome TRAIL resistance. Inhibitor of apoptosis family member survivin is constitutively activated in various cancers and blocks apoptotic signaling. Recently, we demonstrated that YM-155 [3-(2-methoxyethyl)-2-methyl-4,9-dioxo-1-(pyrazin-2-ylmethyl)-4,9-dihydro-3H-naphtho[2,3-d]imidazol-1-ium bromide], a small molecule inhibitor, downregulates not

only survivin in gliomas but also myeloid cell leukemia sequence 1 (Mcl-1), and it upregulates proapoptotic Noxa levels. Because Mcl-1 and survivin are critical mediators of resistance to various anticancer therapies, we questioned whether YM-155 could sensitize resistant glioma cells to TRAIL. To address this hypothesis, we combined YM-155 with TRAIL and examined the effects on cell survival and apoptotic signaling. TRAIL or YM-155 individually induced minimal killing in highly resistant U373 and LN2308 cell lines, but combining TRAIL with YM-155 triggered a synergistic proapoptotic response, mediated through mitochondrial dysfunction via activation of caspases-8, -9, -7, -3, poly-ADP-ribose polymerase, and Bid. Apoptosis induced by combination treatments was blocked by caspase-8 and pan-caspase inhibitors. In addition, knockdown of Mcl-1 by RNA interference overcame apoptotic resistance to TRAIL. Conversely, silencing Noxa by RNA interference reduced the combined effects of YM-155 and TRAIL on apoptosis. Mechanistically, these findings indicate that YM-155 plays a role in counteracting glioma cell resistance to TRAIL-induced apoptosis by downregulating Mcl-1 and survivin and amplifying mitochondrial signaling through intrinsic and extrinsic apoptotic pathways. The significantly enhanced antitumor activity of the combination of YM-155 and TRAIL may have applications for therapy of malignant glioma.

[192]

TÍTULO / TITLE: - Reduction in gamma-Glutamyl Hydrolase Expression Is Associated with Response to Uracil and Tegafur/Leucovorin Chemotherapy in Patients with Colorectal Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3431-8.

AUTORES / AUTHORS: - Sadahiro S; Suzuki T; Tanaka A; Okada K; Kamijo A; Nagase H; Uchida J

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya Isehara, Kanagawa, 259-1193, Japan.

sadahiro@is.icc.u-tokai.ac.jp.

RESUMEN / SUMMARY: - To identify the genes and clinical parameters associated with efficacy of uracil and tegafur/leucovorin (UFT/LV) chemotherapy in colorectal cancer (CRC), we compared the levels of reduced folate in tumors between patients receiving LV and those not receiving LV (study I), and explored the changes in the expression levels of 14 genes after two weeks of UFT/LV chemotherapy in 73 patients with CRC (study II). In study I, the reduced folate levels after LV administration were approximately 3-fold higher than those without LV administration in patients with right-sided tumors or aged >75 years old ($p=0.019$). In study II, the reduction in gamma-glutamyl hydrolase (GGH) expression in responders and in patients with right-sided tumors or aged >75 years old was significantly greater than that in non-responders ($p<0.001$) and in other patients, respectively ($p=0.003$). Increase of

reduced folate and reduction in GGH expression were associated with response to UFT/LV chemotherapy in patients with right-sided tumors or aged >75 years old.

[193]

TÍTULO / TITLE: - Inhibiting Polo-like kinase 1 causes growth reduction and apoptosis in pediatric acute lymphoblastic leukemia cells.

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

REVISTA / JOURNAL: - Haematologica. 2013 Jun 10.

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

[3324/haematol.2013.084434](#)

AUTORES / AUTHORS: - Hartsink-Segers SA; Exalto C; Allen M; Williamson D; Clifford SC; Horstmann M; Caron HN; Pieters R; Den Boer ML

INSTITUCIÓN / INSTITUTION: - Rotterdam, The Netherlands;

RESUMEN / SUMMARY: - This study investigated Polo-like kinase 1, a mitotic regulator often overexpressed in solid tumors and adult hematopoietic malignancies, as a potential new target in the treatment of pediatric acute lymphoblastic leukemia. Polo-like kinase 1 protein and Thr210 phosphorylation levels were higher in pediatric acute lymphoblastic leukemia (N=172) than in normal bone marrow mononuclear cells (N=10) ($p < 0.0001$). High Polo-like kinase 1 protein phosphorylation, but not expression, was associated with a lower probability of event-free survival ($p = 0.042$) and was a borderline significant prognostic factor ($p = 0.065$) in a multivariate analysis including age and initial white blood cell count. Polo-like kinase 1 was necessary for leukemic cell survival, since short hairpin-mediated Polo-like kinase 1 knockdown in acute lymphoblastic leukemia cell lines inhibited cell proliferation by G2/M cell cycle arrest and induced apoptosis through caspase-3 and poly (ADP-ribose) polymerase cleavage. Primary patient cells with a high Polo-like kinase 1 protein expression were sensitive to the Polo-like kinase 1-specific inhibitor NMS-P937 in vitro, whereas cells with a low expression and normal bone marrow cells were resistant. This sensitivity was likely not caused by Polo-like kinase 1 mutations, since only one new mutation (Ser335Arg) was found by 454-sequencing of 38 pediatric acute lymphoblastic leukemia cases. This mutation did not affect Polo-like kinase 1 expression or NMS-P937 sensitivity. Together, these results indicate a pivotal role for Polo-like kinase 1 in pediatric acute lymphoblastic leukemia and show potential for Polo-like kinase 1-inhibiting drugs as an addition to current treatment strategies for cases expressing high Polo-like kinase 1 levels.

[194]

TÍTULO / TITLE: - Induction of sustained deep molecular response in a patient with chronic-phase T315I-mutated chronic myeloid leukemia with interferon-alpha monotherapy.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 25.

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

[3109/10428194.2013.812788](#)

AUTORES / AUTHORS: - Ilander M; Koskenvesa P; Hernesniemi S; Lion T; Porkka K; Mustjoki S

INSTITUCIÓN / INSTITUTION: - Hematology Research Unit Helsinki, Department of Medicine, University of Helsinki and Helsinki University Central Hospital , Helsinki , Finland.

[195]

TÍTULO / TITLE: - A Cyclic Peptide Inhibitor of HIF-1 Heterodimerization That Inhibits Hypoxia Signaling in Cancer Cells.

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

REVISTA / JOURNAL: - J Am Chem Soc. 2013 Jul 17;135(28):10418-25. doi: 10.1021/ja402993u. Epub 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1021/ja402993u](#)

AUTORES / AUTHORS: - Miranda E; Nordgren IK; Male AL; Lawrence CE; Hoakwie F; Cuda F; Court W; Fox KR; Townsend PA; Packham GK; Eccles SA; Tavassoli A

INSTITUCIÓN / INSTITUTION: - Chemistry, double daggerCentre for Biological Sciences, section signInstitute for Life Sciences, University of Southampton , Southampton SO17 1BJ, United Kingdom.

RESUMEN / SUMMARY: - Hypoxia inducible factor-1 (HIF-1) is a heterodimeric transcription factor that acts as the master regulator of cellular response to reduced oxygen levels, thus playing a key role in the adaptation, survival, and progression of tumors. Here we report cyclo-CLLFVY, identified from a library of 3.2 million cyclic hexapeptides using a genetically encoded high-throughput screening platform, as an inhibitor of the HIF-1alpha/HIF-1beta protein-protein interaction in vitro and in cells. The identified compound inhibits HIF-1 dimerization and transcription activity by binding to the PAS-B domain of HIF-1alpha, reducing HIF-1-mediated hypoxia response signaling in a variety of cell lines, without affecting the function of the closely related HIF-2 isoform. The reported cyclic peptide demonstrates the utility of our high-throughput screening platform for the identification of protein-protein interaction inhibitors, and forms the starting point for the development of HIF-1 targeted cancer therapeutics.

[196]

TÍTULO / TITLE: - A specific expression profile of heat-shock proteins and glucose-regulated proteins is associated with response to neoadjuvant chemotherapy in oesophageal adenocarcinomas.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 23;109(2):370-8. doi: 10.1038/bjc.2013.319. Epub 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.319](#)

AUTORES / AUTHORS: - Slotta-Huspenina J; Wolff C; Drecoll E; Feith M; Bettstetter M; Malinowsky K; Bauer L; Becker K; Ott K; Hofler H; Becker KF; Langer R

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, Technische Universität München, Munich, Germany.

RESUMEN / SUMMARY: - Background: Oesophageal adenocarcinomas often show resistances to chemotherapy (CTX), therefore, it would be of high interest to better understand the mechanisms of resistance. We examined the expression of heat-shock proteins (HSPs) and glucose-regulated proteins (GRPs) in pretherapeutic biopsies of oesophageal adenocarcinomas to assess their potential role in CTX response. Methods: Ninety biopsies of locally advanced adenocarcinomas before platinum/5-fluorouracil (FU)-based CTX were investigated by reverse phase protein arrays (RPPAs), immunohistochemistry (IHC) and quantitative RT-PCR. Results: CTX response strongly correlated with survival ($P=0.001$). Two groups of tumours with specific protein expression patterns were identified by RPPA: Group A was characterised by low expression of HSP90, HSP27 and p-HSP27((Ser15, Ser78, Ser82)) and high expression of GRP78, GRP94, HSP70 and HSP60; Group B exhibited the inverse pattern. Tumours of Group A were more likely to respond to CTX, resulting in histopathological tumour regression ($P=0.041$) and post-therapeutic down-categorisation from cT3 to ypT0-T2 ($P=0.040$). High HSP60 protein (IHC) and mRNA expression were also associated with tumour down-categorisation ($P=0.016$ and $P=0.004$). Conclusion: Our findings may enhance the understanding of CTX response mechanisms, might be helpful to predict CTX response and might have translational relevance as they highlight the role of potentially targetable cellular stress proteins in the context of CTX response.

[197]

TÍTULO / TITLE: - Early predictors of oxaliplatin-induced cumulative neuropathy in colorectal cancer patients.

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

REVISTA / JOURNAL: - J Neurol Neurosurg Psychiatry. 2013 Jun 29.

●● Enlace al texto completo (gratis o de pago) [1136/jnnp-2013-305334](#)

AUTORES / AUTHORS: - Velasco R; Bruna J; Briani C; Argyriou AA; Cavaletti G; Alberti P; Frigeni B; Cacciavillani M; Lonardi S; Cortinovis D; Cazzaniga M; Santos C; Kalofonos HP

INSTITUCIÓN / INSTITUTION: - Unit of Neuro-Oncology, Hospital Universitari de Bellvitge-ICO Duran i Reynals, , Barcelona, España.

RESUMEN / SUMMARY: - **OBJECTIVES:** Peripheral neuropathy ranks among the most common dose-limiting and disabling side-effect of oxaliplatin (OXA)-based chemotherapy. The aim of this prospective, multicentre study was to define early clinical and neurophysiological markers that may help to identify patients at risk of developing severe, treatment emergent, cumulative OXA-induced peripheral neuropathy (OXAIPN). **METHODS:** 200 colorectal cancer patients, scheduled to receive OXA-based chemotherapy, were prospectively followed. Detailed neurological assessment employing the clinical Total Neuropathy Score (TNSc), oncological rating scales (National Common Institute-Common Toxicity Criteria V.3) and nerve conduction studies (NCS) were performed at baseline, mid-treatment and at the end of chemotherapy. Symptoms of OXA-induced acute neurotoxicity were systematically recorded. **RESULTS:** According to TNSc, 36 (18%) patients developed grade 3 OXAIPN. These patients were predominantly men ($p=0.005$), presented a significant decrease in all NCS ($p<0.001$), reported more acute neuropathic symptoms ($p<0.001$) and received higher OXA cumulative dose ($p=0.003$). Multivariate analysis showed that three variables obtained at intermediate follow-up, namely, the number of acute symptoms (OR 1.9; CI 95% 1.2 to 3.2; $p=0.012$) and the $>30\%$ decrease in sensory nerve action potential amplitude from the baseline value in radial (OR 41.4; CI 95% 4.98 to 343.1; $p=0.001$) and dorsal sural nerves (OR 24.96; CI 95% 2.6 to 239.4; $p=0.005$) were independently associated with the risk of developing severe OXAIPN. **CONCLUSIONS:** High-grade OXA neurotoxicity can be predicted by clinical and neurophysiological information obtained at mid-treatment. Neurological assessment of acute neuropathy symptoms and radial and dorsal sural nerves NCS should be carefully monitored to predict and hopefully prevent the induction of severe OXAIPN.

[198]

TÍTULO / TITLE: - Identification of the NEDD4L Gene as a Prognostic Marker by Integrated Microarray Analysis of Copy Number and Gene Expression Profiling in Non-small Cell Lung Cancer.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3059-](#)

[6](#)

AUTORES / AUTHORS: - Sakashita H; Inoue H; Akamine S; Ishida T; Inase N; Shirao K; Mori M; Mimori K

INSTITUCIÓN / INSTITUTION: - Department of Molecular and Surgical Oncology, Medical Institute of Bioregulation, Kyushu University, Beppu, Japan.

RESUMEN / SUMMARY: - **PURPOSE:** The purpose of this study was to identify prognostic genes by integrated microarray analysis between comparative

genomic hybridization and gene expression with laser microdissection in non-small cell lung cancer (NSCLC). METHODS: Integrated microarray analysis in 11 lung adenocarcinomas was performed, and several genes were identified. Among them, neural precursor cell-expressed developmentally down-regulated 4-like (NEDD4L) was chosen for further characterization. Quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) was used to explore the clinicopathological significance of NEDD4L expression in 84 NSCLC patients. RESULTS: 18q was more frequently lost in advanced lung cancer. Therefore, we selected the NEDD4L gene, located on chromosome 18q, for which reduced expression was significantly correlated with copy number loss. NEDD4L mRNA expression in paired tumor/normal samples from 79 cases of lung cancer was evaluated using real-time PCR analysis. NEDD4L mRNA expression was significantly lower in tumor tissues than in normal lung tissues ($p < 0.0001$). Clinicopathological factors, such as excessive smoking history, histological grade (moderately and poorly), T stage (T2-4), lymph node metastasis, and pathological stage (stage II-IV), were significantly associated with low NEDD4L expression ($p < 0.05$). In the low expression group, prognoses were significantly poorer than in the high expression group ($p < 0.05$). CONCLUSIONS: Low NEDD4L expression may be a marker of prognosis. This is the first report to describe NEDD4L expression in NSCLC. NEDD4L may be considered a key gene in the progression of NSCLC, and its expression is likely affected by genomic alterations.

[199]

TÍTULO / TITLE: - Efficacy of oncolytic adenovirus expressing suicide genes and interleukin-12 in preclinical model of prostate cancer.

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

REVISTA / JOURNAL: - Gene Ther. 2013 Jul 11. doi: 10.1038/gt.2013.40.

●● [Enlace al texto completo \(gratis o de pago\) 1038/gt.2013.40](#)

AUTORES / AUTHORS: - Freytag SO; Barton KN; Zhang Y

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA.

RESUMEN / SUMMARY: - Oncolytic adenovirus-mediated suicide gene therapy has been shown to improve local tumor control in preclinical tumor models and in the clinic. Although local tumor control is important, for most human cancers, new therapies must also target metastatic disease if they are to have an impact on survival. Here, we test the hypothesis that adding cytokine gene therapy to our multimodal platform improves both local and metastatic tumor control in a preclinical model of prostate cancer. An oncolytic adenovirus (Ad5-yCD/mutTKSR39rep-mIL12) expressing two suicide genes and mouse interleukin-12 (IL-12) was generated. Relative to an adenovirus lacking IL-12 (Ad5-yCD/mutTKSR39rep), Ad5-yCD/mutTKSR39rep-mIL12 improved local and metastatic tumor control in the TRAMP-C2 prostate adenocarcinoma

model, resulting in a significant increase in survival. Ad5-yCD/mutTKSR39rep-mIL12 resulted in high levels of IL-12 and interferon gamma in serum and tumor, increased natural killer (NK) and cytotoxic T-lymphocyte lytic activities, and the development of tumor-specific antitumor immunity. Immune cell depletion studies indicated that both the innate and adaptive arms of immunity were required for maximal Ad5-yCD/mutTKSR39rep-mIL12 activity. The results demonstrate that the addition of IL-12 significantly improves the efficacy of oncolytic adenovirus-mediated suicide gene therapy and provide the scientific basis for future trials targeting locally aggressive cancers. Gene Therapy advance online publication, 11 July 2013; doi:10.1038/gt.2013.40.

[200]

TÍTULO / TITLE: - DMET (Drug-Metabolizing Enzymes and Transporters) microarray analysis of colorectal cancer patients with severe 5-fluorouracil-induced toxicity.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug;72(2):483-8. doi: 10.1007/s00280-013-2210-1. Epub 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2210-1](#)

AUTORES / AUTHORS: - Rumiato E; Boldrin E; Amadori A; Saggioro D

INSTITUCIÓN / INSTITUTION: - Immunology and Molecular Oncology Unit, Veneto Institute of Oncology, IOV-IRCCS, Via Gattamelata 64, 35128, Padova, Italy.

RESUMEN / SUMMARY: - PURPOSE: 5-fluorouracil (5-FU) has been widely used since the 1980s, and it remains the backbone of many chemotherapeutic combination regimens. However, its use is often limited by the occurrence of severe toxicity. Although several reports have shown the detrimental effect of some dihydropyrimidine dehydrogenase (DPYD) and thymidylate synthase (TYMS) gene polymorphisms in patients undergoing 5-FU-based treatment, they account for only a minority of toxicities. METHODS: Looking for new candidate genetic variants associated with 5-FU-induced toxicity, we used the innovative genotyping microarray Affymetrix Drug-Metabolizing Enzymes and Transporters (DMET) Plus GeneChip that interrogates 1,936 genetic variants distributed in 231 genes involved in drug metabolism, excretion, and transport. To reduce variability, we analyzed samples from colorectal cancer patients who underwent fairly homogenous treatments (i.e., Machover or Folfox) and experienced G3 or G4 toxicity; control patients were matched for therapy and selected from those who did not disclose toxicity (G0-G1). RESULTS: Pharmacogenetic genotyping showed no significant difference in DPYD and TYMS genetic variants distribution between cases and controls. However, other polymorphisms could account for 5-FU-induced toxicity, with the CHST1 rs9787901 and GSTM3 rs1799735 having the strongest association. CONCLUSIONS: Although exploratory, this study suggests that genetic

polymorphisms not directly related to 5-FU pharmacokinetics and pharmacodynamics are involved in 5-FU-induced toxicity. Our data also indicates DMET microarray as a valid approach to discover new genetic determinants influencing chemotherapy-induced toxicity.

[201]

TÍTULO / TITLE: - A Sequence Polymorphism in miR-608 Predicts Recurrence after Radiotherapy for Nasopharyngeal Carcinoma.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Aug 2.

- [Enlace al texto completo \(gratis o de pago\) 1158/0008-5472.CAN-13-0395](#)

AUTORES / AUTHORS: - Zheng J; Deng J; Xiao M; Yang L; Zhang L; You Y; Hu M; Li N; Wu H; Li W; Lu J; Zhou Y

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Laboratory of Cancer Molecular Genetics, Medical College of Soochow University; Departments of Radiotherapy & Oncology and Obstetrics and Gynecology, The Second Affiliated Hospital of Soochow University, Suzhou; Department of Otorhinolaryngology-Head and Neck Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou; and The Institute for Chemical Carcinogenesis, The State Key Lab of Respiratory Disease, Guangzhou Medical University, Guangzhou, China.

RESUMEN / SUMMARY: - Nasopharyngeal carcinoma is treated with radiotherapy and other modalities, but there is little information on individual genetic factors to help predict and improve patient outcomes. Single-nucleotide polymorphisms (SNP) in mature microRNA (miRNA) sequences have the potential to exert broad impact as miRNAs target many mRNAs. The aim of this study was to evaluate the effects of SNPs in mature miRNA sequences on clinical outcome in patients with nasopharyngeal carcinoma receiving radiotherapy. In particular, we analyzed associations between seven SNPs and nasopharyngeal carcinoma locoregional recurrence (LRR) in 837 patients from eastern China, validating the findings in an additional 828 patients from southern China. We found that miR-608 rs4919510C>G exhibited a consistent association with LRR in the discovery set [HR, 2.05; 95% confidence interval (CI), 1.35-3.21], the validation set (HR, 2.24; 95% CI, 1.45-3.38), and the combined dataset (HR, 2.08; 95% CI, 1.41-3.26). Biochemical investigations showed that rs4919510C>G affects expression of miR-608 target genes along with nasopharyngeal carcinoma cell growth after irradiation in vivo and in vitro. Notably, X-ray radiation induced more chromatid breaks in lymphocyte cells from rs4919510CC carriers than in those from subjects with other genotypes (P = 0.0024). Our findings reveal rs4919510C>G in miR-608 as a simple marker to predict LRR in patients with radiotherapy-treated nasopharyngeal carcinoma. Cancer Res; 73(16); 1-12.

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[202]

TÍTULO / TITLE: - Pediatric generalized anxiety disorder: predictors of outcome after selective serotonin reuptake inhibitor monotherapy.

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

REVISTA / JOURNAL: - J Clin Psychopharmacol. 2013 Aug;33(4):577-9. doi: 10.1097/JCP.0b013e31829465cb.

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

[1097/JCP.0b013e31829465cb](#)

AUTORES / AUTHORS: - Masi G; Mucci M; Pfanner C; Berloff S; Liboni F; Perugi G

INSTITUCIÓN / INSTITUTION: - IRCCS Stella Maris Scientific Institute of Child Neurology and Psychiatry Calambrone Pisa, Italy gabriele.masi@inpe.unipi.it Department of Psychiatry, Neurobiology Pharmacology and Biotechnologies Psychiatry Section, University of Pisa Pisa, Italy and Institute of Behavioral Sciences "G. De Lisio," Carrara-Pisa, Italy.

[203]

TÍTULO / TITLE: - CCL19, a B-cell chemokine, is related to the decrease of blood memory B-cells and predicts the clinical response to rituximab in rheumatoid arthritis.

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

REVISTA / JOURNAL: - Arthritis Rheum. 2013 Jun 5. doi: 10.1002/art.38023.

●● Enlace al texto completo (gratis o de pago) [1002/art.38023](#)

AUTORES / AUTHORS: - Sellam J; Rouanet S; Hendel-Chavez H; Miceli-Richard C; Combe B; Sibilia J; Le Loet X; Tebib J; Jourdan R; Dougados M; Taoufik Y; Mariette X

INSTITUCIÓN / INSTITUTION: - Rheumatology Department, Saint-Antoine Hospital, Assistance Publique-Hopitaux de Paris (AP-HP), Université Pierre et Marie Curie Paris VI, Paris, France.

RESUMEN / SUMMARY: - Objectives. Migration of B-cells from peripheral blood to the synovium in rheumatoid arthritis (RA) may predict clinical response to rituximab (RTX). This study investigated whether serum levels of chemokines involved in B-cell trafficking are correlated before B-cell depletion with blood memory B-cells or with serum B-cell activation biomarkers and whether chemokine levels predict RTX responsiveness. Methods. RA patients (n=208) received a first course of RTX and EULAR response was evaluated at week 24. Before treatment, blood B-cell subsets were analyzed by flow cytometry (CD27, IgD), and serum B-cell activation biomarkers (rheumatoid factor, anti-CCP, free light chains, IgG, IgA, IgM, and BAFF) were measured. Serum CCL19, CXCL12, CXCL13 chemokine levels were measured by ELISA in the RA patients and in 70 control subjects. Results. All chemokine levels were

increased in RA versus controls and were inversely correlated with CD27+ memory B-cell frequency. CCL19 and CXCL13 levels correlated with 6 and 4 serum B-cell biomarkers, respectively. By univariate analysis, CCL19 level was positively associated with EULAR response (odds ratio = 1.43 [95% confidence interval [CI] 1.08-1.90]; p=0.01). By multivariate analysis, CCL19 predicted RTX response (OR = 1.48 [95% CI: 1.06-2.06]; p=0.02) but not after adjustment for autoantibody status. Conclusion. CXCL13 and CCL19 reflect blood B-cell disturbances and correlate with other serum B-cell biomarkers and therefore represent serum B-cell biomarkers in RA. Serum CCL19 measurement is a new hallmark of B-cell-mediated RA subtype and may predict clinical response to RTX. © 2013 American College of Rheumatology.

[204]

TÍTULO / TITLE: - Malignant Peritoneal Mesothelioma Treated by Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is GLUT1 Expression a Major Prognostic Factor? A Preliminary Study.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3077-](http://dx.doi.org/10.1245/s10434-013-3077-4)

[4](#)

AUTORES / AUTHORS: - Hommell-Fontaine J; Isaac S; Passot G; Decullier E; Traverse-Glehen A; Cotte E; You B; Mohamed F; Gilly FN; Glehen O; Berger F

INSTITUCIÓN / INSTITUTION: - Service de Chirurgie Generale, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Benite, France.

RESUMEN / SUMMARY: - **PURPOSE:** Diffuse malignant peritoneal mesothelioma (DMPM) is a rare primary peritoneal malignancy. Its prognosis has been improved by an aggressive locoregional treatment combining extensive cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Prognostic factors are currently poorly defined for this disease but are essential if treatment is to be standardized. **METHODS:** Twenty-eight patients with DMPM, who were considered preoperatively to be candidates for CRS and HIPEC between June 1998 and August 2010 at our institution, were selected for this study. Medical records and histopathological features were retrospectively reviewed and 24 clinical, histological, and immunohistochemical parameters were assessed for their association with overall survival by univariate and multivariate analyses. **RESULTS:** The following factors were significantly associated with overall survival by univariate analysis: predominant histological growth pattern in the epithelioid areas, nuclear grooves in the epithelioid areas, atypical mitoses, and calretinin and GLUT1 expression by immunohistochemistry in the epithelioid areas. Expression of the facilitative glucose transporter protein GLUT1 in the epithelioid areas was the only factor independently associated with overall survival by multivariate analysis. **CONCLUSIONS:** GLUT1 expression appears to be an indicator of poor

prognosis in DMPM. Standard histological classification of DMPM may not be adequate to select patients for aggressive locoregional treatments, such as CRS and HIPEC. Multicenter validation of the prognostic factors identified in this preliminary study is needed to refine patient selection for potential cure.

[205]

TÍTULO / TITLE: - Prognostic value of combined serum biomarkers in predicting outcomes in cervical cancer patients.

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

REVISTA / JOURNAL: - Clin Chim Acta. 2013 Jul 11;424C:292-297. doi: 10.1016/j.cca.2013.07.003.

●● Enlace al texto completo (gratis o de pago) 1016/j.cca.2013.07.003

AUTORES / AUTHORS: - Li J; Cheng H; Zhang P; Dong Z; Tong HL; Jackie Han JD; Guo F; Tian YP

INSTITUCIÓN / INSTITUTION: - Department of Clinical Biochemistry, State Key Laboratory of Kidney Disease, Chinese PLA General Hospital, Beijing 100853, China.

RESUMEN / SUMMARY: - BACKGROUND: We evaluated the prognostic value of pretreatment serum biomarkers in predicting outcomes in cervical cancer patients subjected to treatment. METHODS: Serum samples collected from 60 cervical cancer patients and 60 age-matched healthy individuals were used for the detection of 22 biomarkers, prior to therapy. Cox multivariate analysis and classification and regression tree analysis (CART) were performed to evaluate the prognostic factors. RESULTS: Cox multivariate analysis disclosed that carbohydrate antigen 153 (CA153), squamous cell carcinoma antigen (SCC) and tumor necrosis factor-alpha (TNF-alpha) are associated with prognosis in cervical cancer. CART analysis led to the stratification of patients into 3 groups: (1) serum concentrations of CA153 ≥ 17.60 mug/l, (2) serum concentrations of CA153 < 17.60 mug/l and TNF-alpha ≥ 10.60 pg/ml, and (3) serum concentrations of CA153 < 17.60 mug/l and TNF-alpha < 10.60 pg/ml. The 2-y overall survival rates for Groups 1, 2 and 3 were 33.3%, 60.0% and 93.9%, respectively. CONCLUSIONS: Higher serum concentrations of TNF-alpha, SCC and CA153 before therapy are independently associated with poor prognosis in patients with stage I and II disease. Combined usage of these three biomarkers allows efficient evaluation of outcomes in cervical cancer patients.

[206]

TÍTULO / TITLE: - TIMP1 overexpression mediates resistance of MCF-7 human breast cancer cells to fulvestrant and down-regulates progesterone receptor expression.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 24.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-0969-](https://doi.org/10.1007/s13277-013-0969-7)

7

AUTORES / AUTHORS: - Bjerre C; Vinther L; Belling KC; Wurtz SO; Yadav R; Lademann U; Rigina O; Do KN; Ditzel HJ; Lykkesfeldt AE; Wang J; Nielsen HB; Brunner N; Gupta R; Schrohl AS; Stenvang J

INSTITUCIÓN / INSTITUTION: - Faculty of Health and Medical Sciences, Department of Veterinary Disease Biology, University of Copenhagen, Dyrlægevej 88, 1, 1870, Frederiksberg C, Denmark.

RESUMEN / SUMMARY: - High levels of Tissue Inhibitor of Metalloproteinases-1 (TIMP1) are associated with poor prognosis, reduced response to chemotherapy, and, potentially, also poor response to endocrine therapy in breast cancer patients. Our objective was to further investigate the hypothesis that TIMP1 is associated with endocrine sensitivity. We established a panel of 11 MCF-7 subclones with a wide range of TIMP1 mRNA and protein expression levels. Cells with high expression of TIMP1 versus low TIMP1 displayed significantly reduced sensitivity to the antiestrogen fulvestrant (ICI 182,780, Faslodex®), while TIMP1 levels did not influence the sensitivity to 4-hydroxytamoxifen. An inverse correlation between expression of the progesterone receptor and TIMP1 was found, but TIMP1 levels did not correlate with estrogen receptor levels or growth-promoting effects of estrogen (estradiol, E2). Additionally, the effects of fulvestrant, 4-hydroxytamoxifen, or estrogen on estrogen receptor expression were not associated with TIMP1 levels. Gene expression analyses revealed associations between expression of TIMP1 and genes involved in metabolic pathways, epidermal growth factor receptor 1/cancer signaling pathways, and cell cycle. Gene and protein expression analyses showed no general defects in estrogen receptor signaling except from lack of progesterone receptor expression and estrogen inducibility in clones with high TIMP1. The present study suggests a relation between high expression level of TIMP1 and loss of progesterone receptor expression combined with fulvestrant resistance. Our findings in vitro may have clinical implications as the data suggest that high tumor levels of TIMP1 may be a predictive biomarker for reduced response to fulvestrant.

[207]

TÍTULO / TITLE: - Interleukin-6 but not tumour necrosis factor-alpha predicts survival in patients with advanced cancer.

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

REVISTA / JOURNAL: - Support Care Cancer. 2013 Jul 5.

- Enlace al texto completo (gratis o de pago) [1007/s00520-013-1878-](https://doi.org/10.1007/s00520-013-1878-4)

4

AUTORES / AUTHORS: - Suh SY; Choi YS; Yeom CH; Kwak SM; Yoon HM; Kim DG; Koh SJ; Park J; Lee MA; Lee YJ; Seo AR; Ahn HY; Yim E

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Dongguk University, Seoul, South Korea.

RESUMEN / SUMMARY: - **PURPOSE:** The purpose of this study was to evaluate the prognostic role of interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) in the survival of patients with advanced cancer. **METHODS:** In this prospective cohort study between three hospice and palliative care centres in South Korea, we followed 98 advanced cancer patients until death or the end of the study. Approximately 60 % of the patients had poor functional status (Eastern Cooperative Oncology Group score ≥ 3). We investigated the symptoms of cancer cachexia anorexia syndrome, possible cytokine-related confounders such as infection and medication records. Influence from clinical variables was adjusted using the Cox proportional hazard model. **RESULTS:** The median survival time was 27 days. On multivariate analysis, elevated IL-6 (hazard ratio, 2.139; $p = 0.003$) was found to be an independent significant prognostic factor. TNF-alpha was not a significant factor. Poor performance status and male gender were also independently related to shortened survival. **CONCLUSIONS:** IL-6 level can be a useful indicator of survival time of patients with advanced cancer at the very end of life. In contrast, the prognostic role of TNF-alpha requires further study.

[208]

TÍTULO / TITLE: - Temporal and spatial evolution of therapy-induced tumor apoptosis detected by caspase-3-selective molecular imaging.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 15;19(14):3914-24. doi: 10.1158/1078-0432.CCR-12-3814. Epub 2013 May 31.

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3814](#)

AUTORES / AUTHORS: - Nguyen QD; Lavdas I; Gubbins J; Smith G; Fortt R; Carroll LS; Graham MA; Aboagye EO

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Department of Surgery and Cancer, Imperial College London Faculty of Medicine, Comprehensive Cancer Imaging Centre, Hammersmith Hospital, London; Post-Graduate Medical Institute, University of Hull, Hull, United Kingdom; and TetraLogic Pharmaceuticals, Malvern, Pennsylvania.

RESUMEN / SUMMARY: - **PURPOSE:** Induction of apoptosis in tumors is considered a desired goal of anticancer therapy. We investigated whether the dynamic temporal and spatial evolution of apoptosis in response to cytotoxic and mechanism-based therapeutics could be detected noninvasively by the caspase-3 radiotracer [(18)F]ICMT-11 and positron emission tomography (PET). **EXPERIMENTAL DESIGN:** The effects of a single dose of the alkylating agent cyclophosphamide (CPA or 4-hydroperoxycyclophosphamide), or the mechanism-based small molecule SMAC mimetic birinapant on caspase-3

activation was assessed in vitro and by [(18)F]ICMT-11-PET in mice bearing 38C13 B-cell lymphoma, HCT116 colon carcinoma, or MDA-MB-231 breast adenocarcinoma tumors. Ex vivo analysis of caspase-3 was compared to the in vivo PET imaging data. RESULTS: Drug treatment increased the mean [(18)F]ICMT-11 tumor uptake with a peak at 24 hours for CPA (40 mg/kg; AUC40-60: 8.04 +/- 1.33 and 16.05 +/- 3.35 %ID/mL x min at baseline and 24 hours, respectively) and 6 hours for birinapant (15 mg/kg; AUC40-60: 20.29 +/- 0.82 and 31.07 +/- 5.66 %ID/mL x min, at baseline and 6 hours, respectively). Voxel-based spatiotemporal analysis of tumor-intrinsic heterogeneity suggested that discrete pockets of caspase-3 activation could be detected by [(18)F]ICMT-11. Increased tumor [(18)F]ICMT-11 uptake was associated with caspase-3 activation measured ex vivo, and early radiotracer uptake predicted apoptosis, distinct from the glucose metabolism with [(18)F]fluorodeoxyglucose-PET, which depicted continuous loss of cell viability. CONCLUSION: The proapoptotic effects of CPA and birinapant resulted in a time-dependent increase in [(18)F]ICMT-11 uptake detected by PET. [(18)F]ICMT-11-PET holds promise as a noninvasive pharmacodynamic biomarker of caspase-3-associated apoptosis in tumors. Clin Cancer Res; 19(14); 3914-24. ©2013 AACR.

[209]

TÍTULO / TITLE: - Circulating CD4-positive lymphocyte levels as predictor of response to induction chemotherapy in patients with advanced laryngeal cancer.

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

REVISTA / JOURNAL: - Head Neck. 2013 Jun 14. doi: 10.1002/hed.23263.

●● [Enlace al texto completo \(gratis o de pago\) 1002/hed.23263](#)

AUTORES / AUTHORS: - Dewyer NA; Wolf GT; Light E; Worden F; Urba S; Eisbruch A; Bradford CR; Chepeha DB; Prince ME; Moyer J; Taylor J

INSTITUCIÓN / INSTITUTION: - The Department of Otolaryngology-Head and Neck Surgery, University of Michigan Schools of Medicine and Public Health, Ann Arbor, Michigan.

RESUMEN / SUMMARY: - Background. Tumor regression after induction chemotherapy (ICT) identifies laryngeal cancers that are responsive to chemoradiation. Patient immune parameters have recently been associated with response to chemotherapy and may identify responding patients. A retrospective analysis was performed to determine if pretreatment, circulating T lymphocyte levels predicted ICT response in patients with advanced laryngeal cancer. Methods. Pretreatment, circulating T lymphocyte subpopulations were correlated with response to therapy and survival. Results were compared with similar data from an identical phase II trial involving patients with oropharyngeal cancer. Results. An increased percentage of CD4+ cells predicted response to ICT and suggested improved survival in patients with laryngeal, but not

oropharyngeal, cancer. In the combined group of patients, increased CD4 levels predicted response to ICT. Conclusion. These findings demonstrate the potential importance of the immune system in chemotherapy response and clinical outcome. Differences in findings between patients with advanced laryngeal and oropharyngeal cancer may reflect different cellular immunity function in the patients with human papillomavirus (HPV)-16+ oropharyngeal cancer. © 2013 Wiley Periodicals, Inc. Head Neck, 2013.

[210]

TÍTULO / TITLE: - Prognostic impact of the number of methylated genes in myelodysplastic syndromes and acute myeloid leukemias treated with azacytidine.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1799-](http://1007/s00277-013-1799-9)

[9](#)

AUTORES / AUTHORS: - Abaigar M; Ramos F; Benito R; Diez-Campelo M; Sanchez-Del-Real J; Hermosin L; Rodriguez JN; Aguilar C; Recio I; Alonso JM; de Las Heras N; Megido M; Fuertes M; Del Canizo MC; Hernandez-Rivas JM

INSTITUCIÓN / INSTITUTION: - Cancer Research Center-IBMCC (USAL-CSIC), Salamanca, España.

RESUMEN / SUMMARY: - The prognostic impact of the aberrant hypermethylation in response to azacytidine (AZA) remains to be determined. Therefore, we have analyzed the influence of the methylation status prior to AZA treatment on the overall survival and clinical response of myeloid malignancies. DNA methylation status of 24 tumor suppressor genes was analyzed by methylation-specific multiplex ligation-dependent probe amplification in 63 patients with myelodysplastic syndromes and acute myeloid leukemia treated with azacytidine. Most patients (73 %) showed methylation of at least one gene, but only 12 % of patients displayed ≥ 3 methylated genes. The multivariate analysis demonstrated that the presence of a high number (≥ 2) of methylated genes ($P = 0.022$), a high WBC count ($P = 0.033$), or anemia ($P = 0.029$) were independent prognostic factors associated with shorter overall survival. The aberrant methylation status did not correlate with the response to AZA, although four of the five patients with ≥ 3 methylated genes did not respond. By contrast, favorable cytogenetics independently influenced the clinical response to AZA as 64.7 % of patients with good-risk cytogenetic abnormalities responded ($P = 0.03$). Aberrant methylation status influences the survival of patients treated with AZA, being shorter in those patients with a high number of methylated genes.

[211]

TÍTULO / TITLE: - EGFR L2 domain mutation is not correlated with resistance to cetuximab in metastatic colorectal cancer patients.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Aug;139(8):1391-6. doi: 10.1007/s00432-013-1454-9. Epub 2013 May 31.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1454-](#)

[9](#)

AUTORES / AUTHORS: - Ito Y; Yamada Y; Asada K; Ushijima T; Iwasa S; Kato K; Hamaguchi T; Shimada Y

INSTITUCIÓN / INSTITUTION: - Department of Clinical Oncology, Yamagata University, 2-2-2 Iidanishi, Yamagata, Yamagata, Japan, i.yuriko@med.id.yamagata-u.ac.jp.

RESUMEN / SUMMARY: - **BACKGROUND:** The KRAS mutation has been associated with resistance to cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, in metastatic colorectal cancer (mCRC). However, the predictive biomarkers of cetuximab resistance in KRAS wild-type mCRC remain unknown except BRAF, NRAS, and PIK3CA exon 20. The objective of the study is to study the impact of EGFR L2 mutations on resistance to cetuximab in KRAS wild-type patients. **PATIENTS AND METHODS:** A total of 247 mCRC patients were screened for KRAS status at the National Cancer Center Hospital between September 2008 and April 2010. We analyzed the EGFR L2 domain mutation status in KRAS wild type and in the patients treated with cetuximab-based therapy. **RESULTS:** There were 136 patients with wild-type KRAS (55 %). Sixty-five patients were analyzed for the L2 domain mutation status, and all patients received cetuximab-based therapy. One patient who had a mutation at exon 9 showed a partial response to cetuximab plus irinotecan. **CONCLUSION:** Mutation of the EGFR L2 domain was analyzed in mCRC patients. Our findings do not provide sufficient evidence that EGFR L2 domain mutation is correlated with resistance to cetuximab.

[212]

TÍTULO / TITLE: - Epidermal growth factor receptor (EGFR) and KRAS mutations during chemotherapy plus anti-EGFR monoclonal antibody treatment in metastatic colorectal cancer.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug;72(2):397-403. doi: 10.1007/s00280-013-2211-0. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2211-](#)

[0](#)

AUTORES / AUTHORS: - Tougeron D; Cortes U; Ferru A; Villalva C; Silvain C; Tourani JM; Levillain P; Karayan-Tapon L

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Poitiers University Hospital, 2 rue de la Miletie, 86000, Poitiers Cedex, France, davidtougeron@hotmail.fr.

RESUMEN / SUMMARY: - It is now well established that metastatic colorectal cancer patients without KRAS mutation (codon 12) benefit from treatment with an epidermal growth factor receptor monoclonal antibody (anti-EGFR mAb). Recently, EFGR and KRAS mutations have been shown to exist in patients who developed resistance to anti-EGFR mAb. We analyzed KRAS, BRAF V600E and EGFR S492R mutations in 37 post-anti-EGFR mAb tumor samples from 23 patients treated with chemotherapy plus anti-EGFR mAb. No EGFR S492R mutation was detected. A KRAS mutation was found after anti-EGFR mAb in only one tumor. Our results suggest that acquired EGFR S492R and KRAS mutations do not constitute the main mechanism of resistance to anti-EGFR mAb in combination with chemotherapy.

[213]

TÍTULO / TITLE: - Intratumoral concentration of estrogens and clinicopathological changes in ductal carcinoma in situ following aromatase inhibitor letrozole treatment.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 9;109(1):100-8. doi: 10.1038/bjc.2013.284. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) 1038/bjc.2013.284

AUTORES / AUTHORS: - Takagi K; Ishida T; Miki Y; Hirakawa H; Kakugawa Y; Amano G; Ebata A; Mori N; Nakamura Y; Watanabe M; Amari M; Ohuchi N; Sasano H; Suzuki T

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Histotechnology, Tohoku University Graduate School of Medicine, 2-1 Seiryomachi, Aoba-ku, 980-8575 Sendai, Japan.

RESUMEN / SUMMARY: - Background: Estrogens have important roles in ductal carcinoma in situ (DCIS) of the breast. However, the significance of presurgical aromatase inhibitor treatment remains unclear. Therefore, we examined intratumoral concentration of estrogens and changes of clinicopathological factors in DCIS after letrozole treatment. Methods: Ten cases of postmenopausal oestrogen receptor (ER)-positive DCIS were examined. They received oral letrozole before the surgery, and the tumour size was evaluated by ultrasonography. Surgical specimens and corresponding biopsy samples were used for immunohistochemistry. Snap-frozen specimens were also available in a subset of cases, and used for hormone assays and microarray analysis. Results: Intratumoral oestrogen levels were significantly lower in DCIS treated with letrozole compared with that in those without the therapy. A great majority of oestrogen-induced genes showed low expression levels in DCIS treated with letrozole by microarray analysis. Moreover, letrozole treatment

reduced the greatest dimension of DCIS, and significantly decreased Ki-67 and progesterone receptor immunoreactivity in DCIS tissues. Conclusion: These results suggest that estrogens are mainly produced by aromatase in DCIS tissues, and aromatase inhibitors potentially inhibit oestrogen actions in postmenopausal ER-positive DCIS through rapid deprivation of intratumoral estrogens.

[214]

TÍTULO / TITLE: - Suppressive effect of nobiletin, a citrus polymethoxyflavonoid that downregulates thioredoxin-interacting protein expression, on tunicamycin-induced apoptosis in SK-N-SH human neuroblastoma cells.

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

REVISTA / JOURNAL: - Neurosci Lett. 2013 Aug 9;549:135-9. doi: 10.1016/j.neulet.2013.06.004. Epub 2013 Jun 14.

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

1016/j.neulet.2013.06.004

AUTORES / AUTHORS: - Ikeda A; Nemoto K; Yoshida C; Miyata S; Mori J; Soejima S; Yokosuka A; Mimaki Y; Ohizumi Y; Degawa M

INSTITUCIÓN / INSTITUTION: - Department of Molecular Toxicology, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan.

RESUMEN / SUMMARY: - Increased expression of thioredoxin-interacting protein (TXNIP) has recently been proved to be a crucial event for irremediable endoplasmic reticulum (ER) stress resulting in the programmed cell death (apoptosis) of pancreatic beta-cells. The present study demonstrated that treatment with 1-10µg/ml tunicamycin, a potent revesant of ER stress, drastically induced TXNIP expression accompanied by the generation of cleaved caspase-3 as an indicator of apoptosis in SK-N-SH human neuroblastoma cells. This result substantiated that TXNIP is also involved in neurodegeneration triggered by ER stress. Moreover, we evaluated the effects of nobiletin, a citrus polymethoxyflavonoid, on tunicamycin-induced apoptosis and TXNIP expression in SK-N-SH cells, because we reported previously that this flavonoid might be able to reduce TXNIP expression. Co-treatment of SK-N-SH cells with 100µM nobiletin and 1µg/ml tunicamycin for 24h strongly suppressed apoptosis and increased TXNIP expression induced by 1µg/ml tunicamycin treatment alone. In addition, we proved that the ability of 100µM nobiletin treatment to reduce TXNIP expression is exerted from 3h after the onset of treatment. Therefore, the protective and ameliorative effects of nobiletin on neuronal degeneration and impaired memory, which several studies using animal models have demonstrated, might arise in part from nobiletin's ability to repress TXNIP expression.

[215]

TÍTULO / TITLE: - Deficiency in expression and epigenetic DNA Methylation of ASS1 gene in nasopharyngeal carcinoma: negative prognostic impact and therapeutic relevance.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1020-](#)

[8](#)

AUTORES / AUTHORS: - Lan J; Tai HC; Lee SW; Chen TJ; Huang HY; Li CF

INSTITUCIÓN / INSTITUTION: - Departments of Pathology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - The risk stratification and final outcomes in patients with nasopharyngeal carcinomas (NPC) still remain suboptimal. Our principal goals were to identify and validate targetable metabolic drivers relevant to pathogenesis of NPC using a published transcriptome. One prominently downregulated gene regulating amino acid metabolism was found to be argininosuccinate synthetase (ASS1). Attributable to epigenetic DNA methylation, ASS1 deficiency may link to the therapeutic sensitivity to the arginine-depriving agents and promote tumor aggressiveness through its newly identified tumor suppressor function. ASS1 immunohistochemistry was therefore examined in a well-defined cohort of 124 NPC biopsy specimens and in the neck lymph node metastases of another ten independent cases. For the latter, bisulphite pyrosequencing was performed to evaluate the extent of ASS1 gene methylation. ASS1 protein deficiency was identified in 64 of 124 cases (51.6 %), significantly related to T3-T4 status ($p = 0.006$), and univariately associated with inferior local recurrence-free survival ($p = 0.0427$), distant metastasis-free survival (DMFS; $p = 0.0036$), and disease-specific survival (DSS; $p = 0.0069$). Together with advanced AJCC stages III-IV, ASS1 protein deficiency was also independently predictive of worse outcomes for the DFMS ($p = 0.010$, hazard ratio = 2.241) and DSS ($p = 0.020$, hazard ratio = 1.900). ASS1 promoter hypermethylation was detected in eight of ten neck nodal metastatic lesions by bisulphite pyrosequencing and associated with ASS1 protein deficiency ($p < 0.001$). In summary, ASS1 protein deficiency was seen in approximately a half of NPCs and associated with advanced T classification, DNA methylation, and clinical aggressiveness, consistent with its tumor suppressor role. This aberration may render pegylated arginine deiminase as a promising strategy for ASS1-deficient NPCs.

[216]

TÍTULO / TITLE: - Nicotinamide N-methyltransferase overexpression is associated with Akt phosphorylation and indicates worse prognosis in patients with nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 11.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s13277-013-0980-](#)

[Z](#)

AUTORES / AUTHORS: - Win KT; Lee SW; Huang HY; Lin LC; Lin CY; Hsing CH; Chen LT; Li CF

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Chi-Mei Medical Center, 901 Chungwa Road, Yung Kang Dist., Tainan County, 710, Taiwan.

RESUMEN / SUMMARY: - Nicotinamide N-methyltransferase (NNMT) is overexpressed in many human cancers and is associated with poor prognosis. Akt (also known as protein kinase B) is an evolutionarily conserved serine/threonine kinase, serving as a downstream effector of the phosphatidylinositol 3-kinase signaling pathway. NNMT was first identified as a differentially upregulated gene in nasopharyngeal cancer tissues through data mining from published transcriptomic databases. Since no prior study has attempted to evaluate the clinical significance of NNMT or phosphorylated Akt (pAkt) expression in nasopharyngeal cancer, this study explores their expression in a large cohort of patients with nasopharyngeal cancer. The study included 124 nasopharyngeal cancer patients who were free of distant metastasis at initial diagnosis. Pathological slides were reviewed and clinical findings collected. We evaluated the expression of NNMT and pAkt immunohistochemically, stratified them into two groups (high and low expression) and examined the correlation with disease-specific survival (DSS), metastasis-free survival (MeFS), local recurrence-free survival (LRFS), and various clinicopathological factors. NNMT expression was significantly positively associated with pAkt expression. The high expression of both markers was significantly associated with an increment of tumor stage ($p = 0.006$ and $p = 0.006$, respectively). High expression of NNMT correlated significantly with a more aggressive clinical course and a significantly shorter DSS. Furthermore, NNMT expression and pAkt expression were strongly predictive of MeFS ($p = 0.008$; $p = 0.0063$) and LRFS ($p = 0.005$; $p = 0.0125$). In multivariate analysis, high expression of NNMT remained as a robust prognosticator for both end points evaluated. It independently portended inferior DSS ($p = 0.02$, HR = 1.976) and worse MeFS ($p = 0.029$, HR = 2.022) after tumor stage ($p = 0.033$, HR = 2.150; $p = 0.028$, HR = 2.942, for DSS and LRFS, respectively). We found NNMT positively correlated with pAkt expression and was independent adverse prognosticators of patient survival. NNMT therefore has potential utility as an indicator for prognosis, predicting treatment response to chemotherapy or radiation therapy, and even as a therapeutic target in the future.

[217]

TÍTULO / TITLE: - mTOR kinase inhibitor sensitizes T-cell lymphoblastic leukemia for chemotherapy-induced DNA damage via suppressing FANCD2 expression.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jul 15. doi: 10.1038/leu.2013.215.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.215](#)

AUTORES / AUTHORS: - Guo F; Li J; Zhang S; Du W; Amarachintha S; Siple J; Phelan J; Grimes HL; Zheng Y; Pang Q

INSTITUCIÓN / INSTITUTION: - Division of Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

[218]

TÍTULO / TITLE: - Induction of G /M phase arrest and apoptosis by the flavonoid tamarixetin on human leukemia cells.

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

REVISTA / JOURNAL: - Mol Carcinog. 2013 Jun 13. doi: 10.1002/mc.22055.

●● Enlace al texto completo (gratis o de pago) [1002/mc.22055](#)

AUTORES / AUTHORS: - Nicolini F; Burmistrova O; Marrero MT; Torres F; Hernandez C; Quintana J; Estevez F

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, España; Instituto Canario de Investigación del Cáncer, Las Palmas de Gran Canaria, España.

RESUMEN / SUMMARY: - Flavonoids are naturally occurring polyphenolic compounds which display a vast array of biological activities. In this study, we investigated the effects of tamarixetin on viability of human tumor cell lines and found that it was cytotoxic against leukemia cells and in particular P-glycoprotein-overexpressing K562/ADR cells. This compound inhibited proliferation in a concentration- and time-dependent manner, induced apoptosis and blocked cell cycle progression at G2 -M phase. This was associated with the accumulation of cyclin B1, Bub1 and p21Cip1/Waf-1, changes in the phosphorylation status of cyclin B1, Cdk1, Cdc25C and MPM-2, and inhibition of tubulin polymerization. Moreover, cell death was found to be associated with cytochrome c release and cleavage of caspases and of poly(ADP-ribose) polymerase, and completely abrogated by the free-radical scavenger N-acetyl-L-cysteine. The sensitivity of leukemic cells to tamarixetin suggests that it should be considered for further preclinical and in vivo testing. © 2013 Wiley Periodicals, Inc.

[219]

TÍTULO / TITLE: - Interferon-beta gene-modified human bone marrow mesenchymal stem cells attenuate hepatocellular carcinoma through inhibiting AKT/FOXO3a pathway.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 25. doi: 10.1038/bjc.2013.422.

●● Enlace al texto completo (gratis o de pago) 1038/bjc.2013.422

AUTORES / AUTHORS: - Xie C; Xie DY; Lin BL; Zhang GL; Wang PP; Peng L; Gao ZL

INSTITUCIÓN / INSTITUTION: - Department of Infectious Diseases, The Third Affiliated Hospital of Sun Yat-Sen University, 600 Tianhe Road, Guangzhou, Guangdong 510630, China.

RESUMEN / SUMMARY: - Objective: This study aims to investigate the use of bone marrow mesenchymal stem cells (BMSCs) genetically engineered to produce interferon-beta (IFN-beta) as a gene delivery system to treat hepatocellular carcinoma (HCC) in vitro and in vivo. Methods: To measure the effects on tumour cell growth in vitro, IFN-beta-producing BMSCs (BMSC/IFN-beta) were co-cultured with the HCC cell line HepG2 and Huh7. Enzyme-linked immunosorbent assay (ELISA) was used to detect the IFN-beta secretion in the BMSC culture condition medium (CM). The effect of BMSC/IFN-beta on HCC cell proliferation was examined both in vitro and in vivo by using MTT, colony formation assay, BrdU staining, cell cycle analysis, and xenografted NOD/SCID mouse tumour model. To examine the impact of BMSC/IFN-beta on the AKT/FOXO3a signalling, RT-PCR and western blotting were performed. Results: The BMSC/IFN-beta cells can stably secrete high levels of IFN-beta. Both MTT and colony forming assay showed that HCC cells had a lower growth rate when cultured in BMSC/IFN-beta-CM as compared with that in BMSC/vector-CM or DMEM culture group. Co-culture with BMSC/IFN-beta-CM dramatically decreased the percentages of cells with incorporated BrdUrd. In BMSC/IFN-beta-CM-treated HCC cells, the proportion of G1-phase cells increased but it decreased in the S phase of the cell. The BMSC/IFN-beta inhibited HCC growth in NOD/SCID mice and prolonged the survival period of these mice. Compared with the control group, p21 and p27 expression of hepatoma cells increased, whereas cyclin D1 and phosphorylation of Rb expression decreased when co-cultured with BMSC/IFN-beta-CM. It was associated with suppression of Akt activity and enhanced transcriptional activity of FOXO3a. Conclusion: The IFN-beta gene-modified BMSCs can effectively inhibit the proliferation of HCC cells in vitro and in vivo through inhibiting the AKT/FOXO3a pathway. These results indicate that BMSC/IFN-beta are a powerful anticancer cytotherapeutic tool for HCC. British Journal of Cancer advance online publication, 25 July 2013; doi:10.1038/bjc.2013.422 www.bjcancer.com.

[220]

TÍTULO / TITLE: - The trefoil factor 1 (TFF1) protein involved in doxorubicin-induced apoptosis resistance is upregulated by estrogen in breast cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 5. doi: 10.3892/or.2013.2593.

- Enlace al texto completo (gratis o de pago) [3892/or.2013.2593](#)

AUTORES / AUTHORS: - Pelden S; Insawang T; Thuwajit C; Thuwajit P

INSTITUCIÓN / INSTITUTION: - Graduate Program in Immunology, Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

RESUMEN / SUMMARY: - Trefoil factor 1 (TFF1) is a small secretory protein expressed in various types of carcinomas including breast cancer. The TFF1 gene contains an estrogen response element and its expression can be regulated by estrogen. Previous reports showed that TFF1 could protect cells from induced apoptosis in vitro. In the present study, the effect of estrogen on the promotion of doxorubicin-induced apoptosis resistance and the role of TFF1 in this process was demonstrated using the MCF-7 breast cancer cell model. Stable knockdown of the TFF1 gene in MCF-7 cells was generated and used to test the sensitivity to doxorubicin treatment compared to mock control cells in the presence or absence of 17beta-estradiol. The apoptotic cells were measured by flow cytometry. The results showed that with the stimulation of apoptosis by doxorubicin, 17beta-estradiol could suppress this process in mock cells but not in TFF1 knockdown cells. Moreover, using a viable cell counting method, it was shown that the anti-TFF1 antibody could reverse the anti-apoptotic effect of estrogen in mock cells and recombinant TFF1 could recover doxorubicin-induced cell death in TFF1 knockdown cells. This process, however, could not be inhibited by fulvestrant, an estrogen antagonist. An apoptosis protein array experiment reflected the role of the anti-oxidative enzyme catalase in estrogen and TFF1-modulated apoptosis and this was confirmed by enzymatic assay. These phenomena determine the role of TFF1 in estrogen-promoted resistance to apoptosis induced by doxorubicin in MCF-7 breast cancer cells. The TFF1 gene may be a target for enhancing the sensitivity to chemotherapy in breast cancer treatment.

[221]

TÍTULO / TITLE: - The Exomes of the NCI-60 Panel: A Genomic Resource for Cancer Biology and Systems Pharmacology.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Jul 15;73(14):4372-82. doi: 10.1158/0008-5472.CAN-12-3342. Epub 2013 Jul 15.

- Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-3342](#)

AUTORES / AUTHORS: - Abaan OD; Polley EC; Davis SR; Zhu YJ; Bilke S; Walker RL; Pineda M; Gindin Y; Jiang Y; Reinhold WC; Holbeck SL; Simon RM; Doroshow JH; Pommier Y; Meltzer PS

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Genetics Branch; Laboratory of Molecular Pharmacology, Center for Cancer Research; and Division of

Cancer Treatment and Diagnosis, National Cancer Institute, NIH, Bethesda, Maryland.

RESUMEN / SUMMARY: - The NCI-60 cell lines are the most frequently studied human tumor cell lines in cancer research. This panel has generated the most extensive cancer pharmacology database worldwide. In addition, these cell lines have been intensely investigated, providing a unique platform for hypothesis-driven research focused on enhancing our understanding of tumor biology. Here, we report a comprehensive analysis of coding variants in the NCI-60 panel of cell lines identified by whole exome sequencing, providing a list of possible cancer specific variants for the community. Furthermore, we identify pharmacogenomic correlations between specific variants in genes such as TP53, BRAF, ERBBs, and ATAD5 and anticancer agents such as nutlin, vemurafenib, erlotinib, and bleomycin showing one of many ways the data could be used to validate and generate novel hypotheses for further investigation. As new cancer genes are identified through large-scale sequencing studies, the data presented here for the NCI-60 will be an invaluable resource for identifying cell lines with mutations in such genes for hypothesis-driven research. To enhance the utility of the data for the greater research community, the genomic variants are freely available in different formats and from multiple sources including the CellMiner and Ingenuity websites. Cancer Res; 73(14); 4372-82. ©2013 AACR.

[222]

TÍTULO / TITLE: - Systemic Retinoids for the Chemoprevention of Cutaneous Squamous Cell Carcinoma and Verrucal Keratosis in a Cohort of Patients on BRAF inhibitors.

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

REVISTA / JOURNAL: - Br J Dermatol. 2013 Jul 20. doi: 10.1111/bjd.12519.

●● Enlace al texto completo (gratis o de pago) [1111/bjd.12519](#)

AUTORES / AUTHORS: - Anforth R; Blumetti TC; Clements A; Kefford R; Long GV; Fernandez-Penas P

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, Westmead Hospital, Westmead, Australia; Sydney Medical School, The University of Sydney, Sydney, Australia.

RESUMEN / SUMMARY: - BACKGROUND: The treatment of metastatic melanoma has changed greatly with the development of inhibitors targeted at the mutated BRAF kinase present in up to 50% of metastatic melanoma. These agents, vemurafenib and dabrafenib have been shown to increase median survival. Unfortunately, they have also been associated with the development of verrucal keratosis (VK) and cutaneous squamous cell carcinoma (cuSCC). These lesions require surgical excision, and when a large number of these lesions need to be treated, it can significantly affect the patient's quality of life. OBJECTIVES: To determine if acitretin is suitable as a chemopreventative

agent for the development of verrucal keratosis and cuSCC, in patients on BRAF inhibitors. METHODS: Patients treated with the BRAF inhibitor vemurafenib or dabrafenib for stage IV metastatic melanoma, who had more than five surgical excisions to remove lesions suggestive of cuSCC, were offered the opportunity to commence acitretin as a chemopreventative agent. Patients were evaluated every 4 weeks. Clinical and histological data was collected. RESULTS: A total of eight patients, who had a total of 24 cuSCC removed, were included in the study. After commencement of acitretin, only five cuSCC were excised from two patients. The most significant reduction was in a patient who had developed 13 cuSCC over 10 months and only two cuSCC three months after commencing acitretin. No modifications in the dose of the BRAFi were made as a result of cuSCC in any of these patients. CONCLUSIONS: Acitretin should be considered as a chemopreventative agent for VK and cuSCC, in patients taking BRAF inhibitors, before considering dosage reductions. This article is protected by copyright. All rights reserved.

[223]

TÍTULO / TITLE: - Overexpression of stathmin 1 is associated with poor prognosis of patients with gastric cancer.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 13.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-0882-](http://1007/s13277-013-0882-0)

[0](#)

AUTORES / AUTHORS: - Ke B; Wu LL; Liu N; Zhang RP; Wang CL; Liang H

INSTITUCIÓN / INSTITUTION: - Department of Gastric Cancer, Tianjin Medical University Cancer Hospital and City Key Laboratory of Tianjin Cancer Center, Tianjin, 300060, China.

RESUMEN / SUMMARY: - Recently, stathmin 1 has been proposed to function as an oncogene based on some relevant studies in multiple types of human cancers. However, the role of stathmin 1 in gastric cancer carcinogenesis has not been elucidated yet. The aim of this study was to investigate the expression of stathmin 1 as well as its association with overall survival of gastric cancer patients. The expression of stathmin 1 was detected by real-time quantitative reverse transcription polymerase chain reaction and Western blotting in gastric cancer and adjacent nontumor tissues. In addition, stathmin 1 expression was analyzed by immunohistochemistry in paraffin samples from 210 primary gastric cancer patients. The expression levels of stathmin 1 mRNA and protein in gastric cancer tissues were both significantly higher than those in adjacent nontumor tissues. In addition, the expression of stathmin 1 is correlated with Lauren's classification, depth of invasion, lymph node metastases, and tumor node metastasis (TNM) stage (all $P < 0.05$). Univariate analysis showed that high stathmin 1 expression was associated with poor prognosis in gastric cancer patients ($P = 0.040$). Multivariate analysis demonstrated that only lymph

node metastasis and TNM stage were the independent prognostic indicators for gastric cancer. Stathmin 1 expression status is not an independent prognostic factor for patients with gastric cancer. Further subgroup analysis revealed that stathmin 1 expression was significantly correlated with prognosis in diffuse type gastric cancer. This research showed that the stathmin 1 overexpression might play an important role in the pathogenesis and subsequent progression of gastric cancer. Stathmin 1 could also be a potential therapeutic target in gastric cancer, especially for diffuse type gastric cancer.

[224]

TÍTULO / TITLE: - Next-generation sequencing of paired tyrosine kinase inhibitor-sensitive and -resistant EGFR mutant lung cancer cell lines identifies spectrum of DNA changes associated with drug resistance.

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

REVISTA / JOURNAL: - Genome Res. 2013 Aug 5.

●● [Enlace al texto completo \(gratis o de pago\) 1101/gr.152322.112](#)

AUTORES / AUTHORS: - Jia P; Jin H; Meador CB; Xia J; Ohashi K; Liu L; Pirazzoli V; Dahlman KB; Politi K; Michor F; Zhao Z; Pao W

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Informatics.

RESUMEN / SUMMARY: - Somatic mutations in kinase genes are associated with sensitivity of solid tumors to kinase inhibitors, but patients with metastatic cancer eventually develop disease progression. In EGFR mutant lung cancer, modeling of acquired resistance (AR) with drug-sensitive cell lines has identified clinically relevant EGFR tyrosine kinase inhibitor (TKI) resistance mechanisms such as the second-site mutation, EGFR T790M, amplification of the gene encoding an alternative kinase, MET, and epithelial-mesenchymal transition (EMT). The full spectrum of DNA changes associated with AR remains unknown. We used next-generation sequencing to characterize mutational changes associated with four populations of EGFR mutant drug-sensitive and five matched drug-resistant cell lines. Comparing resistant cells with parental counterparts, 18-91 coding SNVs/indels were predicted to be acquired and 1-27 were lost; few SNVs/indels were shared across resistant lines. Comparison of two related parental lines revealed no unique coding SNVs/indels, suggesting that changes in the resistant lines were due to drug selection. Surprisingly, we observed more CNV changes across all resistant lines, and the line with EMT displayed significantly higher levels of CNV changes than the other lines with AR. These results demonstrate a framework for studying the evolution of AR and provide the first genome-wide spectrum of mutations associated with the development of cellular drug resistance in an oncogene-addicted cancer. Collectively, the data suggest that CNV changes may play a larger role than previously appreciated in the acquisition of drug resistance and highlight that resistance may be heterogeneous in the context of different tumor cell backgrounds.

[225]

TÍTULO / TITLE: - Oncogenic PIK3CA gene mutations and HER2/neu gene amplifications determine the sensitivity of uterine serous carcinoma cell lines to GDC-0980, a selective inhibitor of Class I PI3 kinase and mTOR kinase (TORC1/2).

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

REVISTA / JOURNAL: - Am J Obstet Gynecol. 2013 Jul 24. pii: S0002-9378(13)00752-7. doi: 10.1016/j.ajog.2013.07.020.

●● Enlace al texto completo (gratis o de pago) 1016/j.ajog.2013.07.020

AUTORES / AUTHORS: - English DP; Bellone S; Cocco E; Bortolomai I; Pecorelli S; Lopez S; Silasi DA; 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 PIK3CA mutational status and c-erbB2 gene amplification in a series of primary uterine serous carcinomas (USC) cell lines. To assess the efficacy of GDC-0980, a potent inhibitor of Class I PI3 kinase and mTOR kinase (TORC1/2), against primary USC harboring HER2/neu gene amplification and/or PIK3CA mutations. STUDY DESIGN: Twenty-two primary USC cell lines were evaluated for c-erbB2 oncogene amplification by FISH assays and for PIK3CA gene mutations by direct DNA sequencing of exons 9 and 20. In vitro sensitivity to GDC-0980 was evaluated by flow-cytometry-based viability and proliferation assays. Downstream cellular responses to GDC-0980 were assessed by measuring phosphorylation of the 4-EBP1 protein by flow-cytometry. RESULTS: Five of 22 (22.7%) USC cell lines contained oncogenic PIK3CA mutations while 9 (40.9%) harbored c-erbB2 gene amplification by FISH. GDC-0980 caused a strong differential growth inhibition in FISH positive USC when compared to FISH negative (GDC-0980 IC50 mean \pm SEM= 0.29 \pm 0.05 μ M in FISH+ versus 1.09 \pm 0.20 μ M in FISH-tumors, P = 0.02). FISH positive USC harboring PIK3CA mutations were significantly more sensitive to GDC-0980 exposure when compared to USC cell lines harboring wild type PIK3CA (P = 0.03). GDC-0980 growth-inhibition was associated with a significant and dose-dependent decline in phosphorylated 4-EBP1 levels. CONCLUSIONS: Oncogenic PIK3CA mutations and c-erbB2 gene amplification may represent biomarkers to identify patients harboring USC who may benefit most from the use of GDC-0980.

[226]

TÍTULO / TITLE: - Retrospective Analysis of 235 Unselected Patients with Mantle Cell Lymphoma (MCL) confirms prognostic relevance of MIPI (MCL

International Prognostic Index), and Ki-67 in the Era of Rituximab: Long-Term Data from the Czech Lymphoma Project Database.

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

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

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

[3109/10428194.2013.815349](#)

AUTORES / AUTHORS: - Salek D; Vesela P; Boudova L; Janikova A; Klener P; Vokurka S; Jankovska M; Pytlik R; Belada D; Pirnos J; Moulis M; Kodet R; Michal M; Janousova E; Muzik J; Mayer J; Trneny M

RESUMEN / SUMMARY: - ABSTRACT Although a prognostic model (MIPI=MCL International prognostic Index) for patients with mantle cell lymphoma (MCL) was established, its clinical significance for daily practice in the rituximab era remains controversial. Data of 235 unselected MCL patients from the Czech Lymphoma Group Database were analysed. MIPI, simplified MIPI (s-MIPI) and Ki-67 proliferation index were assessed for all patients and for subgroup of 155 rituximab-treated (RT) patients. MIPI divided all patients into subgroups of low-risk (22%), intermediate-risk (29%) and high-risk (49%) with median overall survival: 105.8 vs. 54.1 vs. 24.6 months ($p < 0.001$). S-MIPI revealed similar results. The validity of both indexes was confirmed in (RT) patients. We confirmed Ki-67 index to be a powerful single prognostic factor for overall survival (64.4 vs. 20.1 months, $p < 0.001$) for all patients and for (RT) subset. Our results confirmed clinical relevance of MIPI, s-MIPI, and Ki-67 for risk stratification in MCL also in the rituximab era.

[227]

TÍTULO / TITLE: - Prostate cancer cells differ in testosterone accumulation, dihydrotestosterone conversion, and androgen receptor signaling response to steroid 5alpha-reductase inhibitors.

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

REVISTA / JOURNAL: - Prostate. 2013 Jun 27. doi: 10.1002/pros.22694.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22694](#)

AUTORES / AUTHORS: - Wu Y; Godoy A; Azzouni F; Wilton JH; Ip C; Mohler JL

INSTITUCIÓN / INSTITUTION: - Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, New York; Department of Urology, Roswell Park Cancer Institute, Buffalo, New York.

RESUMEN / SUMMARY: - BACKGROUND: Blocking 5alpha-reductase-mediated testosterone conversion to dihydrotestosterone (DHT) with finasteride or dutasteride is the driving hypothesis behind two prostate cancer prevention trials. Factors affecting intracellular androgen levels and the androgen receptor (AR) signaling axis need to be examined systematically in order to fully understand the outcome of interventions using these drugs. METHODS: The expression of three 5alpha-reductase isozymes, as determined by immunohistochemistry and qRT-PCR, was studied in five human prostate

cancer cell lines. Intracellular testosterone and DHT were analyzed using mass spectrometry. A luciferase reporter assay and AR-regulated genes were used to evaluate the modulation of AR activity. RESULTS: Prostate cancer cells were capable of accumulating testosterone to a level 15-50 times higher than that in the medium. The profile and expression of 5alpha-reductase isozymes did not predict the capacity to convert testosterone to DHT. Finasteride and dutasteride were able to depress testosterone uptake in addition to lowering intracellular DHT. The inhibition of AR activity following drug treatment often exceeded the expected response due to reduced availability of DHT. The ability to maintain high intracellular testosterone might compensate for the shortage of DHT. CONCLUSIONS: The biological effect of finasteride or dutasteride appears to be complex and may depend on the interplay of several factors, which include testosterone turnover, enzymology of DHT production, ability to use testosterone and DHT interchangeably, and propensity of cells for off-target AR inhibitory effect. Prostate © 2013 Wiley Periodicals, Inc.

[228]

TÍTULO / TITLE: - p53 Expression in Pretreatment Specimen Predicts Response to Neoadjuvant Chemotherapy Including Anthracycline and Taxane in Patients with Primary Breast Cancer.

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

REVISTA / JOURNAL: - Acta Med Okayama. 2013 Jun;67(3):165-70.

AUTORES / AUTHORS: - Shien T; Kinoshita T; Seki K; Yoshida M; Hojo T; Shimizu C; Taira N; Doihara H; Akashi-Tanaka S; Tsuda H; Fujiwara Y

INSTITUCIÓN / INSTITUTION: - Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama 700-8558, Japan.tshien@md.okayama-u.ac.jp.

RESUMEN / SUMMARY: - While clinical and pathologic responses are important prognostic parameters, biological markers from core needle biopsy (CNB) are needed to predict neoadjuvant chemotherapy (NAC) response, to individualize treatment, and to achieve maximal efficacy. We retrospectively evaluated the cases of 183 patients with primary breast cancer who underwent surgery after NAC (anthracycline and taxane) at the National Cancer Center Hospital (NCCH). We analyzed EGFR, HER2, and p53 expression and common clinicopathological features from the CNB and surgical specimens of these patients. These biological markers were compared between sensitive patients (pathological complete response;pCR) and insensitive patients (clinical no change;cNC and clinical progressive disease;cPD). In a comparison between the 9 (5%) sensitive patients and 30 (16%) insensitive patients, overexpression of p53 but not overexpression of either HER2 or EGFR was associated with a good response to NAC. p53 (p0.045) and histological grade 3 (p0.011) were important and significant predictors of the response to NAC. The correspondence rates for histological type, histological grade 3, ER, PgR,

HER2, p53, and EGFR in insensitive patients between CNB and surgical specimens were 70%, 73%, 67%, 70%, 80%, 93%, and 73%. The pathologic response was significantly associated with p53 expression and histological grade 3. The correspondence rate of p53 expression between CNB and surgical specimens was higher than that of other factors. We conclude that the level of p53 expression in the CNB was an effective and reliable predictor of treatment response to NAC.

[229]

TÍTULO / TITLE: - Incidence and predictors of febrile neutropenia during chemotherapy in patients with head and neck cancer.

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

REVISTA / JOURNAL: - Support Care Cancer. 2013 Jun 8.

●● Enlace al texto completo (gratis o de pago) [1007/s00520-013-1873-](#)

[9](#)

AUTORES / AUTHORS: - Takenaka Y; Cho H; Yamamoto M; Nakahara S; Yamamoto Y; Inohara H

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan, ytakenaka@ent.med.osaka-u.ac.jp.

RESUMEN / SUMMARY: - **PURPOSE:** Febrile neutropenia (FN) is an oncologic emergency, and its management is critical during chemotherapy. However, little is known about FN in patients with head and neck cancer. The purpose of this study was to investigate the incidence and predictors of FN in patients with head and neck cancer. **METHODS:** We performed a retrospective study in a university hospital in Japan between January 2008 and December 2012. Head and neck cancer patients treated with a platinum-based regimen were included in the analysis. **RESULTS:** FN occurred in 47 out of 138 cycles, and the incidence of FN was highest during the first cycle. Severe sepsis or more serious events were observed in 46 % of FN episodes. Patients treated with TPF (docetaxel, cisplatin, and fluorouracil) were more susceptible to FN than those treated with DC (docetaxel, cisplatin). The patient-specific risk factors revealed using univariate analysis were tube feeding, the presence of diabetes mellitus, and gastrointestinal adverse effects. Of these, logistic regression analysis demonstrated tube feeding and diabetes mellitus as independent predictors of FN. **CONCLUSIONS:** The incidence of FN in head and neck cancer patients in the community setting is higher than previously reported. Patients receiving enteral nutrition and those with diabetes are at high risk for FN.

[230]

TÍTULO / TITLE: - Prognostic Significance of K- ras Codon 12 Mutation in Patients with Resected Gallbladder Cancer.

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

REVISTA / JOURNAL: - Dig Surg. 2013 Jul 6;30(3):240-246.

●● Enlace al texto completo (gratis o de pago) [1159/000353133](#)

AUTORES / AUTHORS: - Kazmi HR; Chandra A; Nigam J; Noushif M; Parmar D; Gupta V

INSTITUCIÓN / INSTITUTION: - Department of Surgical Gastroenterology, King George's Medical University, Indian Institute of Toxicology Research (IITR), Lucknow, India.

RESUMEN / SUMMARY: - Background: Point mutation of K-ras is associated with carcinogenesis and overall survival in various cancers. We investigated the mutational spectrum of K-ras codon 12 in resected normal and gallbladder cancer tissue samples in a Northern Indian population and correlated it with different clinicopathological parameters. Patients and Methods: Gallbladder tissues from normal (n = 24) and cancer patients (n = 39) were analyzed for K-ras codon 12 mutation by restriction fragment length polymorphism. Statistical analysis was carried out using the chi² test or Fisher's exact test. Survival was estimated using the Kaplan-Meier method, and the difference between survival curves was analyzed by the log-rank test. Results: The frequency of K-ras mutation was significantly higher (p = 0.001) in gallbladder cancer tissue samples (16/39) compared to normal samples (1/24). Patients with K-ras mutation had a significantly decreased overall survival (p = 0.003), particularly for stage II (p = 0.021) and III (p = 0.009) cancers. No significant correlation was observed with any of the other clinicopathological factors studied. Conclusions: Gallbladder cancer has a high frequency of K-ras codon 12 mutation with poorer outcomes in resected stage II and III disease. K-ras mutational analysis has important prognostic implications that need to be investigated further.

[231]

TÍTULO / TITLE: - Inhibition of vacuolar H⁺ ATPase enhances sensitivity to tamoxifen via up-regulation of CHOP in breast cancer cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Aug 2;437(3):463-8. doi: 10.1016/j.bbrc.2013.06.106. Epub 2013 Jul 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.06.106](#)

AUTORES / AUTHORS: - Jin HO; Lee YH; Kim HA; Kim EK; Noh WC; Kim YS; Hwang CS; Kim JI; Chang YH; Hong SI; Hong YJ; Park IC; Lee JK

INSTITUCIÓN / INSTITUTION: - Laboratory of Biospecimen Management & Research, Korea Institute of Radiological & Medical Sciences, 215-4 Gongneung-dong, Nowon-gu, Seoul 139-709, Republic of Korea; Division of Radiation Cancer Research, Korea Institute of Radiological & Medical Sciences, 215-4 Gongneung-dong, Nowon-gu, Seoul 139-706, Republic of Korea.

RESUMEN / SUMMARY: - Resistance of estrogen receptor-positive breast cancer cells to tamoxifen represents a major barrier to the successful treatment of breast cancer. In the present study, we found that vacuolar H⁺ ATPase (vATPase) inhibitors, bafilomycin A1 and concanamycin A, sensitize tamoxifen-induced cell death. siRNA targeting ATP6V0C, a 16-kDa hydrophobic proteolipid subunit of vATPase that plays a central role in H⁺ transport, markedly increased cell death induced by tamoxifen. Interestingly, bafilomycin A1 induced up-regulation of DR4/DR5 and CHOP. Knock-down of CHOP by siRNA suppressed the cell death induced by bafilomycin A1 and tamoxifen, suggesting that bafilomycin A1-mediated CHOP activation sensitizes to tamoxifen. In addition, we found that bafilomycin A1 enhances TRAIL-induced cell death in breast cancer cells. Furthermore, we showed that combination of vATPase inhibitors with tamoxifen also effectively induced cell death in HER2- and ERalpha-overexpressing breast cancer cells. Overall, our results demonstrate that inhibition of vATPase can potentiate the apoptotic effects of tamoxifen through up-regulation of CHOP.

[232]

TÍTULO / TITLE: - A panel of four cytokines predicts the prognosis of patients with malignant gliomas.

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

REVISTA / JOURNAL: - J Neurooncol. 2013 Jun 8.

- Enlace al texto completo (gratis o de pago) [1007/s11060-013-1171-](http://1007/s11060-013-1171-x)

[X](#)

AUTORES / AUTHORS: - Lin Y; Zhang G; Zhang J; Gao G; Li M; Chen Y; Wang J; Li G; Song SW; Qiu X; Wang Y; Jiang T

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, 1st Affiliated Hospital, China Medical University, Shenyang, 110001, People's Republic of China, lilylinyi@gmail.com.

RESUMEN / SUMMARY: - A comprehensive evaluation of cytokine levels in patients with gliomas could provide important information for the progression and host responses of gliomas. We studied a panel of 120 cytokines and growth factors and investigated their prognostic values for glioma. A protein antibody array was first performed to study the prognostic significance of 120 cytokines in the plasma samples of 45 glioblastoma patients prior to craniotomy or biopsy procedure. An independent set of plasma samples from 260 patients with astrocytomas (80 grade II, 80 grade III, 100 grade IV) with complete clinicopathologic data and follow-ups were used for validation. Ten cytokines were identified by significance analysis of microarray, in which four were associated with poor prognosis (IL-15, MCP-1, GDNF, IL-1R4/ST2), and six were associated with good prognosis (IGFBP-6, MIP-1delta, ICAM-3, IL-7, MIP-3beta, and sgp130) of the glioblastoma patients. Moreover, a 4-cytokine panel composed of IL-7, IL1R4/ST2, sgp130 and MCP-1 showed significant

correlation with overall survival of the glioblastoma patients (HR 2.068; 95 % CI 1.357-3.153; p = 0.001). In the validation set, the cytokine panel was significantly correlated with overall survival in the 260 glioma patients (HR 3.480, 95 % CI 1.890-6.422) in multivariate Cox regression analysis. It also showed strong correlation with survival in patients with malignant gliomas (grade III: HR 2.790, 95 % CI 1.597-3.984, p = 0.002; grade IV: HR 1.753; 95 % CI 1.502-2.255, p < 0.001). This panel of four cytokines: IL-7, IL1R4/ST2, sgp130, and MCP-1 can serve as a prognostic marker for patients with malignant gliomas.

[233]

TÍTULO / TITLE: - The aromatase inhibitors (plus ovarian function suppression) in premenopausal breast cancer patients: Ready for prime time?

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

REVISTA / JOURNAL: - Cancer Treat Rev. 2013 May 29. pii: S0305-7372(13)00092-3. doi: 10.1016/j.ctrv.2013.04.007.

●● Enlace al texto completo (gratis o de pago) 1016/j.ctrv.2013.04.007

AUTORES / AUTHORS: - Montagna E; Canello G; Colleoni M

INSTITUCIÓN / INSTITUTION: - Division of Medical Senology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. Electronic address: emilia.montagna@ieo.it.

RESUMEN / SUMMARY: - Tamoxifen alone or the combination of ovarian function suppression (OFS) and tamoxifen are the mainstay of hormonal therapy in premenopausal women with endocrine-responsive breast cancer. The results of large trials conducted with the third generation of aromatase inhibitors (AIs) in the metastatic, neoadjuvant and adjuvant setting, indicated better outcomes among postmenopausal breast cancer patients with endocrine responsive disease given AIs than among those given tamoxifen. These results supported the investigation of AIs in combination with OFS in premenopausal women with hormone receptor positive breast cancer. In this article we reviewed the efficacy and toxicity data on the use of AIs combined with OFS in premenopausal breast cancer patients in metastatic, neoadjuvant and adjuvant setting. Given the available evidence at the time in metastatic setting for premenopausal patients suitable of endocrine therapy the AI is a viable option, if tamoxifen resistance is proven, although mandates the use of OFS. In neoadjuvant setting the AIs in combination of OFS should not be used outside of a clinical trial. In the adjuvant setting, tamoxifen alone or OFS plus tamoxifen are reasonable options. Despite the lack of conclusive data favoring the combination of tamoxifen plus OFS, this treatment might be a reasonable option for subgroups of patients such as very young patients, OFS alone should not be considered unless tamoxifen was contraindicated. Similarly, in cases where tamoxifen is contraindicated, AIs as an adjunct to OFS is a treatment option in

premenopausal patients. New large randomized studies are required to confirm the role of OFS plus an AI in premenopausal women.

[234]

TÍTULO / TITLE: - Induction of apoptosis in T lymphoma cells by long-term treatment with thyroxine involves PKCzeta nitration by nitric oxide synthase.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0869-](#)

[8](#)

AUTORES / AUTHORS: - Barreiro Arcos ML; Sterle HA; Vercelli C; Valli E; Cayrol MF; Klecha AJ; Paulazo MA; Diaz Flaque MC; Franchi AM; Cremaschi GA

INSTITUCIÓN / INSTITUTION: - Instituto de Investigaciones Biomedicas, Facultad de Ciencias Medicas, Pontificia Universidad Catolica Argentina (UCA), CONICET, Alicia M. de Justo 1600 3 degrees piso, CABA, Buenos Aires, Argentina.

RESUMEN / SUMMARY: - Thyroid hormones are important regulators of cell physiology, inducing cell proliferation, differentiation or apoptosis, depending on the cell type. Thyroid hormones induce proliferation in short-term T lymphocyte cultures. In this study, we assessed the effect of long-term thyroxine (T4) treatment on the balance of proliferation and apoptosis and the intermediate participants in T lymphoma cells. Treatment with T4 affected this balance from the fifth day of culture, inhibiting proliferation in a time-dependent manner. This effect was associated with apoptosis induction, as characterized through nuclear morphological changes, DNA fragmentation, and Annexin V-FITC/Propidium Iodide co-staining. In addition, increased iNOS gene and protein levels, and enzyme activity were observed. The generation of reactive oxygen species, depolarization of the mitochondrial membrane, and a reduction in glutathione levels were also observed. The imbalance between oxidants and antioxidants species is typically associated with the nitration of proteins, including PKCzeta, an isoenzyme essential for lymphoma cell division and survival. Consistently, evidence of PKCzeta nitration via proteasome degradation was also observed in this study. Taken together, these results suggest that the long-term culture of T lymphoma cells with T4 induces apoptosis through the increased production of oxidative species resulting from both augmented iNOS activity and the loss of mitochondrial function. These species induce the nitration of proteins involved in cell viability, promoting proteasome degradation. Furthermore, we discuss the impact of these results on the modulation of T lymphoma growth and the thyroid status in vivo.

[235]

TÍTULO / TITLE: - (4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methanone inhibits tubulin polymerization, induces G/M arrest, and triggers apoptosis in human leukemia HL-60 cells.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Jun 10. pii: S0041-008X(13)00264-0. doi: 10.1016/j.taap.2013.06.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.06.001](#)

AUTORES / AUTHORS: - Magalhaes HI; Wilke DV; Bezerra DP; Cavalcanti BC; Rotta R; de Lima DP; Beatriz A; Moraes MO; Diniz-Filho J; Pessoa C

INSTITUCIÓN / INSTITUTION: - Departamento de Fisiologia e Farmacologia, Faculdade de Medicina, Universidade Federal do Ceara, Fortaleza, Ceara, Brazil.

RESUMEN / SUMMARY: - (4-Methoxyphenyl)(3,4,5-trimethoxyphenyl)methanone (PHT) is a known cytotoxic compound belonging to the phenstatin family. However, the exact mechanism of action of PHT-induced cell death remains to be determined. The aim of this study was to investigate the mechanisms underlying PHT-induced cytotoxicity. We found that PHT displayed potent cytotoxicity in different tumor cell lines, showing IC50 values in the nanomolar range. Cell cycle arrest in G2/M phase along with the augmented metaphase cells was found. Cells treated with PHT also showed typical hallmarks of apoptosis such as cell shrinkage, chromatin condensation, phosphatidylserine exposure, increase of the caspase 3/7 and 8 activation, loss of mitochondrial membrane potential, and internucleosomal DNA fragmentation without affecting membrane integrity. Studies conducted with isolated tubulin and docking models confirmed that PHT binds to the colchicine site and interferes in the polymerization of microtubules. These results demonstrated that PHT inhibits tubulin polymerization, arrests cancer cells in G2/M phase of the cell cycle, and induces their apoptosis, exhibiting promising anticancer therapeutic potential.

[236]

TÍTULO / TITLE: - The beta5/focal adhesion kinase/glycogen synthase kinase 3beta integrin pathway in high-grade osteosarcoma: a protein expression profile predictive of response to neoadjuvant chemotherapy.

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

REVISTA / JOURNAL: - Hum Pathol. 2013 Jul 8. pii: S0046-8177(13)00177-9. doi: 10.1016/j.humpath.2013.03.020.

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

[1016/j.humpath.2013.03.020](#)

AUTORES / AUTHORS: - Le Guellec S; Moyal EC; Filleron T; Delisle MB; Chevreau C; Rubie H; Castex MP; de Gauzy JS; Bonneville P; Gomez-Brouchet A

INSTITUCIÓN / INSTITUTION: - Service d'anatomie et cytologie pathologiques, CHU Rangueil, Toulouse, France 50032.

RESUMEN / SUMMARY: - To date, chemosensitivity to neoadjuvant chemotherapy of patients with high-grade osteosarcoma is evaluated on surgical resection by evaluation of the percentage of necrotic cells. As yet, no predictive profile of response to chemotherapy has been used in clinical practice. Because we have previously shown that the integrin pathway controls genotoxic-induced cell death and hypoxia, we hypothesized that in primary biopsies, expression of proteins involved in this pathway could be associated with sensitivity to neoadjuvant chemotherapy in high-grade osteosarcoma. We studied beta1, beta3, and beta5 integrin expression and integrin-linked kinase, focal adhesion kinase (FAK), glycogen synthase kinase 3beta (GSK3beta), Rho B, angiopoietin-2, beta-catenin, and ezrin expression by immunohistochemistry in 36 biopsies of osteosarcomas obtained before treatment. All patients received a chemotherapy regimen in the neoadjuvant setting. An immunoreactive score was assessed, combining the percentage of positive tumor cells and staining intensity. We evaluated the correlation of the biomarkers with response to chemotherapy, metastasis-free survival, and overall survival. A combination of 3 biomarkers (beta5 integrin, FAK, and GSK3beta) discriminated good and poor responders to chemotherapy, with the highest area under the curve (89.9%; 95% confidence interval, 77.4-1.00) and a diagnostic accuracy of 90.3%. Moreover, high expression of ezrin was associated with an increased risk of metastasis (hazard ratio, 3.93; 95% confidence interval, 1.19-12.9; P = .024). We report a protein expression profile in high-grade osteosarcoma associating beta5 integrin, FAK, and GSK3beta that significantly correlates with poor response to neoadjuvant chemotherapy. This biomarker profile could help select patients for whom an alternative protocol using inhibitors of this pathway can be proposed.

[237]

TÍTULO / TITLE: - Impact of chemotherapy and radiotherapy for testicular germ cell tumors on spermatogenesis and sperm DNA: a multicenter prospective study from the CECOS network.

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

REVISTA / JOURNAL: - Fertil Steril. 2013 Jun 8. pii: S0015-0282(13)00616-X. doi: 10.1016/j.fertnstert.2013.05.018.

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

[1016/j.fertnstert.2013.05.018](#)

AUTORES / AUTHORS: - Bujan L; Walschaerts M; Moinard N; Hennebicq S; Saias J; Brugnol F; Auger J; Berthaut I; Szerman E; Daudin M; Rives N

INSTITUCIÓN / INSTITUTION: - Federation Francaise des Centre d'Etude et de Conservation des OEufs et du Sperme Humains (CECOS), France; Universite de Toulouse; UPS; Groupe de Recherche en Fertilité Humaine (EA 3694, Human Fertility Research Group), CECOS, Toulouse, France. Electronic address: bujan.l@chu-toulouse.fr.

RESUMEN / SUMMARY: - OBJECTIVE: To determine the consequences of adjuvant testicular germ cell tumor treatment (TGCT) on sperm characteristics and sperm DNA, and to evaluate the predictors of sperm recovery. DESIGN: Multicenter prospective longitudinal study of patients analyzed before treatment and after 3, 6, 12, and 24 months. SETTING: University hospitals. PATIENT(S): One hundred twenty-nine volunteer TGCT patients and a control group of 257 fertile men. INTERVENTION(S): Routine semen analyses, sperm DNA, and chromatin assessments. MAIN OUTCOME MEASURE(S): Comparisons of mean sperm characteristics before and after treatment, with sperm recovery analyzed by the Kaplan-Meier method. RESULT(S): The quantitative and qualitative sperm characteristics decreased after treatment, with lowest values at 3 and 6 months and with variations according to treatment type. The mean total sperm count recovered to pretreatment values at 12 months after treatment after two or fewer bleomycin, etoposide, and cisplatin (BEP) cycles, but not after radiotherapy or more than two BEP cycles. Only the treatment modalities and pretreatment sperm production were related to recovery of the World Health Organization reference sperm values. An increased proportion of patients had elevated high sperm DNA stainability at 6 months after radiotherapy. CONCLUSION(S): Adjuvant treatments for testicular germ cell tumor have drastic effects on spermatogenesis and sperm chromatin quality. These new data on both the recovery period according to treatment modalities and the post-treatment chromatin status of sperm are useful tools for counseling patients wishing to conceive.

[238]

TÍTULO / TITLE: - Novel recombinant human b7-h4 antibodies overcome tumoral immune escape to potentiate T-cell antitumor responses.

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

REVISTA / JOURNAL: - Cancer Res. 2013 Aug 1;73(15):4820-9. doi: 10.1158/0008-5472.CAN-12-3457. Epub 2013 May 30.

●● Enlace al texto completo (gratis o de pago) [1158/0008-5472.CAN-12-3457](#)

AUTORES / AUTHORS: - Dangaj D; Lanitis E; Zhao A; Joshi S; Cheng Y; Sandaltzopoulos R; Ra HJ; Danet-Desnoyers G; Powell DJ Jr; Scholler N

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Department of Obstetrics and Gynecology, Ovarian Cancer Research Center, and Departments of Pathology and Laboratory Medicine and Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Department of Molecular Biology and Genetics, Democritus University of Thrace, Alexandroupolis, Greece; and SRI International, Menlo Park, CA.

RESUMEN / SUMMARY: - B7-H4 (VTCN1, B7x, B7s) is a ligand for inhibitory coreceptors on T cells implicated in antigenic tolerization. B7-H4 is expressed by tumor cells and tumor-associated macrophages (TAM), but its potential

contributions to tumoral immune escape and therapeutic targeting have been less studied. To interrogate B7-H4 expression on tumor cells, we analyzed fresh primary ovarian cancer cells collected from patient ascites and solid tumors, and established cell lines before and after in vivo passaging. B7-H4 expression was detected on the surface of all fresh primary human tumors and tumor xenotransplants, but not on most established cell lines, and B7-H4 was lost rapidly by tumor xenograft cells after short-term in vitro culture. These results indicated an in vivo requirement for B7-H4 induction and defined conditions for targeting studies. To generate anti-B7-H4-targeting reagents, we isolated antibodies by differential cell screening of a yeast-display single-chain fragments variable (scFv) library derived from patients with ovarian cancer. We identified anti-B7-H4 scFv that reversed in vitro inhibition of CD3-stimulated T cells by B7-H4 protein. Notably, these reagents rescued tumor antigen-specific T-cell activation, which was otherwise inhibited by coculture with antigen-loaded B7-H4+ APCs, B7-H4+ tumor cells, or B7-H4- tumor cells mixed with B7-H4+ TAMs; peritoneal administration of anti-B7-H4 scFv delayed the growth of established tumors. Together, our findings showed that cell surface expression of B7-H4 occurs only in tumors in vivo and that antibody binding of B7-H4 could restore antitumor T-cell responses. We suggest that blocking of B7-H4/B7-H4 ligand interactions may represent a feasible therapeutic strategy for ovarian cancer. *Cancer Res*; 73(15); 4820-9. ©2013 AACR.

[239]

TÍTULO / TITLE: - Polyphenol tri-vanillic ester 13c inhibits P-JAK2V617F and Bcr-Abl oncokinas expression in correlation with STAT3/STAT5 inactivation and apoptosis induction in human leukemia cells.

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

REVISTA / JOURNAL: - *Cancer Lett.* 2013 Jun 26. pii: S0304-3835(13)00473-4. doi: 10.1016/j.canlet.2013.06.023.

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

1016/j.canlet.2013.06.023

AUTORES / AUTHORS: - Trecul A; Morceau F; Gaigneaux A; Orsini M; Chateauvieux S; Grandjenette C; Lamoral-Theys D; Ionescu A; Kiss R; Dicato M; Diederich M

INSTITUCIÓN / INSTITUTION: - Laboratoire de Biologie Moleculaire et Cellulaire du Cancer, Hopital Kirchberg, 9, Rue Edward Steichen, 2540 Luxembourg, Luxembourg.

RESUMEN / SUMMARY: - Constitutive activity of kinases has been reported in many types of cancers, so that inhibition of “onco-kinases” became a validated anti-cancer strategy. We found that the polyphenol 13c, a tri-vanillate derivative, inhibited kinase phosphorylation in leukemia cells. P-JAK2, P-Src and P-PI3Kp85 inhibition occurred independently of phosphatase involvement in JAK2V617F expressing HEL cells while 13c inhibited Bcr-Abl expression

without inhibition of phosphorylation in chronic myelogenous cell lines (K562, MEG-01). In correlation with kinase inhibition, 13c abolished constitutive P-STAT3/P-STAT5 expression, down-regulated Mcl-1 and c-Myc gene expression and induced apoptosis. Altogether, polyphenol 13c displays potential antitumor activities by affecting onco-kinases and STAT activities.

[240]

TÍTULO / TITLE: - Asparagine synthetase is an independent predictor of surgical survival and a potential therapeutic target in hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 9;109(1):14-23. doi: 10.1038/bjc.2013.293. Epub 2013 Jun 13.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.293](#)

AUTORES / AUTHORS: - Zhang B; Dong LW; Tan YX; Zhang J; Pan YF; Yang C; Li MH; Ding ZW; Liu LJ; Jiang TY; Yang JH; Wang HY

INSTITUCIÓN / INSTITUTION: - 1] International Cooperation Laboratory on Signal Transduction, Eastern Hepatobiliary Surgery Institute, Second Military Medical University, 225 Changhai Road, Shanghai 200438, People's Republic of China [2] Department of Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225 Changhai Road, Shanghai 200438, People's Republic of China.

RESUMEN / SUMMARY: - Background:Asparagine synthetase (ASNS) is associated with drug resistance in leukaemia, and the function of this enzyme in the context of hepatocellular carcinoma (HCC) is not clear. In this study, the relationship between ASNS expression and clinical outcomes after surgical resection was investigated, and the therapeutic value of ASNS was also evaluated.Methods:The expression of ASNS was evaluated in HCC samples by real-time PCR and immunohistochemistry assays. The correlation between ASNS expression and clinicopathological features was investigated. Potential clinicopathological prognostic factors were examined by univariate and multivariate survival analysis. Asparagine synthetase was overexpressed and knocked down in HCC cell lines to assess the influence of the enzyme on cell proliferation, migration and tumourigenicity. L-asparaginase was used to treat HCC cells with high or low levels of ASNS in vitro and in vivo to examine the therapeutic efficacy.Results:The expression of ASNS was higher in HCC tumour tissues and was closely correlated with the serum AFP level, tumour size, microscopic vascular invasion, tumour encapsulation, TNM stage and BCLC stage. Patients with low ASNS expression levels had a poor prognosis with respect to overall survival (OS). The multivariate survival analysis indicated that ASNS is an independent prognostic factor for OS. Furthermore, functional studies demonstrated that ASNS significantly inhibits the proliferation, migration and tumourigenicity of HCC cells. The knockdown of ASNS markedly increased sensitivity to L-asparaginase, indicating that cells with different ASNS protein

levels have different sensitivities to L-asparaginase. Conclusion: The expression of ASNS is an independent factor affecting the survival of HCC patients, and low ASNS expression in HCC was correlated with worse surgical outcomes. The ASNS may be a promising therapeutic target for the treatment of HCC.

[241]

TÍTULO / TITLE: - Urokinase Plasminogen Activator and Its Inhibitor Type-1 as Prognostic Factors in Differentiated Thyroid Carcinoma Patients.

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

REVISTA / JOURNAL: - Otolaryngol Head Neck Surg. 2013 Jul 8.

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

[1177/0194599813496374](#)

AUTORES / AUTHORS: - Horvatic Herceg G; Herceg D; Kralik M; Kulic A; Bence-Zigman Z; Tomic-Brzac H; Bracic I; Kusacic-Kuna S; Prgomet D

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine and Radiation Protection, University Hospital Center Zagreb, Zagreb, Croatia.

RESUMEN / SUMMARY: - Objective To investigate the prognostic value of urokinase-type plasminogen activator (uPA) and its inhibitor, type-1 plasminogen activator inhibitor (PAI-1), in differentiated thyroid cancer. Study Design Prospective cohort study. Setting University hospital. Subjects and Methods Cytosolic concentrations of uPA and PAI-1 were determined in 105 patients with differentiated thyroid carcinoma and normal matched tissues using an enzyme-linked immunoassay (ELISA). Results Both uPA and PAI-1 concentrations were significantly higher in differentiated thyroid tumors (uPA = 0.509 +/- 0.767 and PAI-1 = 6.337 +/- 6.415 ng/mg) compared to normal tissues (uPA = 0.237 +/- 0.051, P < .001; PAI-1 = 2.368 +/- 0.418 ng/mg, P < .001). uPA and PAI-1 were significantly higher if extrathyroidal invasion (uPA, P = .015; PAI-1, P < .001) or distant metastasis (PAI-1 P < .001) was present, as well as in tumors whose size exceeded 1 cm in diameter (uPA, P = .002; PAI-1, P = .001). Survival analysis revealed the significant impact of both uPA and PAI-1 on progression-free survival (PFS) (82.22 vs 49.478 months for patients with low and high uPA, respectively, P < .001; 87.068 vs 44.964 months for patients with low and high PAI-1, respectively, P < .001). Univariate analysis showed that gender, tumor size, tumor grade, extrathyroid invasion, local lymph node involvement, distant metastasis, uPA, and PAI-1 were significant predictors of PFS. However, multivariate analysis identified only distant metastasis and tumor tissue uPA and PAI-1 as independent prognostic factors. Conclusion These findings indicate that high uPA and PAI-1 levels represent independent unfavorable prognostic factors in patients with differentiated thyroid carcinoma.

[242]

TÍTULO / TITLE: - Comparison of prognostic models for patients with diffuse large B-cell lymphoma in the rituximab era.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jun 18.

●● Enlace al texto completo (gratis o de pago) 1007/s00277-013-1807-0

AUTORES / AUTHORS: - Huang YC; Liu CY; Lu HJ; Liu HT; Hung MH; Hong YC; Hsiao LT; Gau JP; Liu JH; Hsu HC; Chiou TJ; Chen PM; Tzeng CH; Yu YB

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Medical Oncology, Department of Medicine, Taipei Veterans General Hospital, Taoyuan Branch, Taoyuan, Taiwan, Republic of China.

RESUMEN / SUMMARY: - Several revisions of International Prognostic Index (IPI) have been proposed for patients with diffuse large B-cell lymphoma (DLBCL) after the introduction of rituximab. Expanding evidence suggests that baseline absolute lymphocyte count (ALC) is also an independent factor for outcome prediction. We investigated the optimal prognostic model for these patients in the rituximab era. The study enrolled 274 consecutive patients with DLBCL receiving first-line cyclophosphamide, doxorubicin, vincristine, and prednisone based chemotherapy with rituximab between 2003 and 2009. Five factors within IPI and ALC were entered for Cox regression analysis. Overall survival (OS) and progression-free survival were calculated for different risk groups of models. Efficacy of models was compared by the value of Akaike information criterion (AIC). Revised IPI (R-IPI) and ALC/R-IPI, but not IPI, were informative to discriminate between different risk groups. In multivariate analysis for individual factors of the prognostic models, performance status >1 [odds ratio (OR) 3.59], Ann Arbor stage III or IV (OR 2.24), and ALC <1 x 10⁹/L (OR, 2.75) remained significant. Another modified score based on the three factors divided patients into four risk groups and the 3-year OS rate was 93, 77, 39, and 13 %, respectively. By comparing AIC values in the Cox proportional hazards model, the modified three-factor model was the superior prognostic model followed by established ALC/R-IPI, R-IPI, and standard IPI. In conclusion, the addition of the novel factor, ALC, interacts with other established factors in outcome prediction for DLBCL. Development of a new score is needed for a better risk stratification in the rituximab era and would be helpful in the design of future clinical trials. The proposed three-factor model should be validated in large-scale studies.

[243]

TÍTULO / TITLE: - Using doxorubicin and siRNA-loaded heptapeptide-conjugated nanoparticles to enhance chemosensitization in epidermal growth factor receptor high-expressed breast cancer cells.

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

REVISTA / JOURNAL: - J Drug Target. 2013 Jul 5.

- Enlace al texto completo (gratis o de pago)

[3109/1061186X.2013.811511](#)

AUTORES / AUTHORS: - Liu CW; Lin WJ

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Pharmaceutical Sciences, School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan and.

RESUMEN / SUMMARY: - Abstract The aim of this study was to develop the heptapeptide-conjugated active targeting nanoparticles for delivery of doxorubicin and siRNA to epidermal growth factor receptor (EGFR) high-expressed breast cancer cells. The active targeting nanoparticles were prepared by using a synthesized poly(D,L-lactide-co-glycolide)-poly(ethylene glycol) (PLGA-PEG) copolymer conjugated with a heptapeptide. The particle size of peptide-conjugated nanoparticles was less than 200 nm with narrow size distribution and the surface charge was negative. The uptake of peptide-conjugated nanoparticles was more efficient in EGFR high-expressed MDA-MB-468 cells than in EGFR low-expressed HepG2 cells by 3.9 folds due to peptide specific binding to EGF receptor followed by EGF receptor-mediated endocytosis. The nanoparticles were used to deliver doxorubicin and siRNA, and their in vitro release was faster in pH 4.0 (500 U lipase) than in pH 7.4. The IC50 of doxorubicin-loaded peptide-conjugated nanoparticles was lower than that of peptide-free nanoparticles by 2.3 folds in MDA-MB-468 cells. Similarly, the cellular growth inhibition of siRNA/DOTAP-loaded peptide-conjugated nanoparticles was 2.1 folds higher than that of peptide-free nanoparticles. In conclusion, the heptapeptide-conjugated PLGA-PEG nanoparticles provided active targeting potential to EGFR high-expressed MDA-MB-468 breast cancer cells, and a synergistic cytotoxicity effect was achieved by co-delivery of doxorubicin and siRNA/DOTAP-loaded peptide-conjugated nanoparticles.

[244]

TÍTULO / TITLE: - An Undesired Effect of Chemotherapy: GEMCITABINE PROMOTES PANCREATIC CANCER CELL INVASIVENESS THROUGH REACTIVE OXYGEN SPECIES-DEPENDENT, NUCLEAR FACTOR κ B- AND HYPOXIA-INDUCIBLE FACTOR 1 α -MEDIATED UP-REGULATION OF CXCR4.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jul 19;288(29):21197-207. doi: 10.1074/jbc.M113.484576. Epub 2013 Jun 5.

- Enlace al texto completo (gratis o de pago) [1074/jbc.M113.484576](#)

AUTORES / AUTHORS: - Arora S; Bhardwaj A; Singh S; Srivastava SK; McClellan S; Nirodi CS; Piazza GA; Grizzle WE; Owen LB; Singh AP

INSTITUCIÓN / INSTITUTION: - From the Department of Oncologic Sciences, Mitchell Cancer Institute, University of South Alabama, Mobile, Alabama 36604.

RESUMEN / SUMMARY: - Recently, we have shown that CXCL12/CXCR4 signaling plays an important role in gemcitabine resistance of pancreatic cancer (PC) cells. Here, we explored the effect of gemcitabine on this resistance mechanism. Our data demonstrate that gemcitabine induces CXCR4 expression in two PC cell lines (MiaPaCa and Colo357) in a dose- and time-dependent manner. Gemcitabine-induced CXCR4 expression is dependent on reactive oxygen species (ROS) generation because it is abrogated by pretreatment of PC cells with the free radical scavenger N-acetyl-L-cysteine. CXCR4 up-regulation by gemcitabine correlates with time-dependent accumulation of NF-kappaB and HIF-1alpha in the nucleus. Enhanced binding of NF-kappaB and HIF-1alpha to the CXCR4 promoter is observed in gemcitabine-treated PC cells, whereas their silencing by RNA interference causes suppression of gemcitabine-induced CXCR4 expression. ROS induction upon gemcitabine treatment precedes the nuclear accumulation of NF-kappaB and HIF-1alpha, and suppression of ROS diminishes these effects. The effect of ROS on NF-kappaB and HIF-1alpha is mediated through activation of ERK1/2 and Akt, and their pharmacological inhibition also suppresses gemcitabine-induced CXCR4 up-regulation. Interestingly, our data demonstrate that nuclear accumulation of NF-kappaB results from phosphorylation-induced degradation of IkkappaBalpha, whereas HIF-1alpha up-regulation is NF-kappaB-dependent. Lastly, our data demonstrate that gemcitabine-treated PC cells are more motile and exhibit significantly greater invasiveness against a CXCL12 gradient. Together, these findings reinforce the role of CXCL12/CXCR4 signaling in gemcitabine resistance and point toward an unintended and undesired effect of chemotherapy.

[245]

TÍTULO / TITLE: - Impact of physical size on gefitinib efficacy in patients with non-small cell lung cancer harboring EGFR mutations.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Jun 25. pii: S0169-5002(13)00254-7. doi: 10.1016/j.lungcan.2013.05.021.

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

[1016/j.lungcan.2013.05.021](#)

AUTORES / AUTHORS: - Ichihara E; Hotta K; Takigawa N; Kudo K; Kato Y; Honda Y; Hayakawa H; Minami D; Sato A; Tabata M; Tanimoto M; Kiura K

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Oncology, and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Japan. Electronic address: ichihae@md.okayama-u.ac.jp.

RESUMEN / SUMMARY: - Gefitinib is an essential drug for the treatment of non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) gene mutations. The approved dosage is 250mg/body/day without adjustment

for physical size such as body surface area (BSA), and the impact of physical size on the efficacy of gefitinib has not been evaluated. Here, we sought to clarify this issue using a retrospective cohort. We reviewed the medical records of patients with consecutive advanced NSCLC harboring EGFR mutations who underwent gefitinib monotherapy at Okayama University Hospital. In total, 101 patients were included in this study, and the median BSA in this cohort was 1.5m². The median progression-free survival (PFS) of the patients with higher BSA ($\geq 1.5\text{m}^2$) was significantly worse than that of those with lower BSA ($< 1.5\text{m}^2$) (10.4 vs. 18.0 months; $p=0.019$, log-rank test). Multivariate analysis also showed a significant impact of BSA on PFS (hazards ratio, 2.34; 95% confidence interval, 1.78-2.89; $p=0.002$). By contrast, no significant association between BSA and PFS was observed in those undergoing cytotoxic chemotherapy (4.0 vs. 5.1 months; $p=0.989$, log-rank test), suggesting that BSA is a predictive, rather than a prognostic, marker for gefitinib therapy in EGFR-mutated NSCLC. In conclusion, BSA affected PFS in patients with EGFR-mutated NSCLC who underwent gefitinib monotherapy, suggesting the need for appraisal of BSA-based dose adjustment, even for this molecular target-based therapy.

[246]

TÍTULO / TITLE: - Androgen receptor enhances entosis, a non-apoptotic cell death, through modulation of Rho/ROCK pathway in prostate cancer cells.

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

REVISTA / JOURNAL: - Prostate. 2013 Sep;73(12):1306-15. doi: 10.1002/pros.22676. Epub 2013 Jun 15.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22676](#)

AUTORES / AUTHORS: - Wen S; Shang Z; Zhu S; Chang C; Niu Y

INSTITUCIÓN / INSTITUTION: - Chawnshang Chang Sex Hormone Research Center, Tianjin Institute of Urology, Tianjin Medical University, Tianjin, China.

RESUMEN / SUMMARY: - BACKGROUND: Cell-in-cell phenomenon has been found for more than a century. Entosis, which is a newly found homogeneous cell-in-cell phenomenon and a non-apoptosis cell death progress, has unclear function in prostate cancer progression. Here, we dissected mechanism of AR signaling related to entosis incidence in PCa progression. METHODS: Two stable PCa cell lines, named LNCaP-ARsi and C4-2-ARsi were established with stably transfected AR-shRNA to knockdown AR mRNA expression in LNCaP and C4-2 cells, respectively. PC3-AR9 cell line was also established after stably transfecting full-length AR-cDNA into PC3 cells. All these cells were cultured in poly-HEME-coated plates to induce entosis, which is demonstrated via double staining. RESULTS: Androgen-DHT could enhance entosis in LNCaP, C4-2 and PC3-AR9 PCa cells in a dose dependent manner. Knock-down of AR in LNCaP and C4-2 significantly suppressed entosis as compared to LNCaP-ARsc and C4-2-ARsc cells at both 1 and 10 nM DHT condition ($P <$

0.05). And suppression of Rho/ROCK expression resulted in interruption of AR-mediated entosis. Human PCa samples surveys demonstrated that entosis was found only in CRPC but not in BPH and ADPC where AR was less expressed as compared to CRPC. CONCLUSIONS: These results indicated that AR might play a negative role during PCa progression via influencing entosis by modulating Rho/ROCK pathway. This newly identified AR role of enhancing entosis might help us to better understand the multiple and opposite roles of AR, which could either promote or suppress PCa cell progression via different mechanisms. Prostate 73: 1306-1315, 2013. © 2013 Wiley Periodicals, Inc.

[247]

TÍTULO / TITLE: - Differential role of thiopurine methyltransferase in the cytotoxic effects of 6-mercaptopurine and 6-thioguanine on human leukemia cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 26;437(2):280-6. doi: 10.1016/j.bbrc.2013.06.067. Epub 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.06.067

AUTORES / AUTHORS: - Karim H; Ghalali A; Lafolie P; Vitols S; Fotoohi AK

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Clinical Pharmacology Unit, Karolinska Institutet, SE-171 76 Stockholm, Sweden. Electronic address: hazhar.i.karim@gmail.com.

RESUMEN / SUMMARY: - The thiopurine antimetabolites, 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) are inactive pro-drugs that require intracellular metabolism for activation to cytotoxic metabolites. Thiopurine methyltransferase (TPMT) is one of the most important enzymes in this process metabolizing both 6-MP and 6-TG to different methylated metabolites including methylthioinosine monophosphate (meTIMP) and methylthioguanosine monophosphate (meTGMP), respectively, with different suggested pharmacological and cytotoxic properties. While meTIMP is a potent inhibitor of de novo purine synthesis (DNPS) and significantly contributes to the cytotoxic effects of 6-MP, meTGMP, does not add much to the effects of 6-TG, and the cytotoxicity of 6-TG seems to be more dependent on incorporation of thioguanine nucleotides (TGNs) into DNA rather than inhibition of DNPS. In order to investigate the role of TPMT in metabolism and thus, cytotoxic effects of 6-MP and 6-TG, we knocked down the expression of the gene encoding the TPMT enzyme using specifically designed small interference RNA (siRNA) in human MOLT4 leukemia cells. The knock-down was confirmed at RNA, protein, and enzyme function levels. Apoptosis was determined using annexin V and propidium iodide staining and FACS analysis. The results showed a 34% increase in sensitivity of MOLT4 cells to 1µM 6-TG after treatment with TPMT-targeting siRNA, as compared to cells transfected with non-targeting siRNA, while the sensitivity of the cells toward 6-MP was not affected significantly by down-regulation of the TPMT gene. This differential contribution of the enzyme TPMT

to the cytotoxicity of the two thiopurines is probably due to its role in formation of the meTIMP, the cytotoxic methylated metabolite of 6-MP, while in case of 6-TG methylation by TPMT substantially deactivates the drug.

[248]

TÍTULO / TITLE: - Molecular profiling of stroma identifies Osteopontin as an independent predictor of poor prognosis in intrahepatic cholangiocarcinoma.

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

REVISTA / JOURNAL: - Hepatology. 2013 Jun 14. doi: 10.1002/hep.26577.

●● Enlace al texto completo (gratis o de pago) [1002/hep.26577](#)

AUTORES / AUTHORS: - Sulpice L; Rayar M; Desille M; Turlin B; Fautrel A; Boucher E; Llamas-Gutierrez F; Meunier B; Boudjema K; Clement B; Coulouarn C

INSTITUCIÓN / INSTITUTION: - Inserm, UMR991, Liver Metabolisms and Cancer, F-35033 Rennes, France; Université de Rennes 1, F-35043 Rennes, France; CHU Rennes, Service de Chirurgie Hépatobiliaire et Digestive, F-35033 Rennes, France.

RESUMEN / SUMMARY: - Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary cancer in the liver. ICC is an aggressive cancer with poor prognosis and limited therapeutic strategies. The identification of new drug targets and prognostic biomarkers is an important clinical challenge for ICC. The presence of an abundant stroma is a histological hallmark of ICC. Given the well established role of the stromal compartment in the progression of cancer diseases, we hypothesized that relevant biomarkers could be identified by analyzing the stroma of ICC. By combining laser capture microdissection and gene expression profiling we demonstrated that ICC stromal cells exhibit dramatic genomic changes. We identified a signature of 1,073 non-redundant genes that significantly discriminate the tumor stroma from non tumor fibrous tissue. Functional analysis of differentially expressed genes demonstrated that up-regulated genes in the stroma of ICC were related to cell cycle, extracellular matrix (ECM) and Transforming Growth Factor beta (TGFbeta) pathways. Tissue microarray analysis using an independent cohort of 40 ICC patients validated at a protein level the increase expression of Collagen 4^{α1}/COL4A1, Laminin gamma 2/LAMC2, Osteopontin/SPP1, KIAA0101 and TGFbeta2 genes in the stroma of ICC. Statistical analysis of clinical and pathological features demonstrated that the expression of Osteopontin, TGFbeta2 and Laminin in the stroma of ICC was significantly correlated with patient overall survival. More importantly, multivariate analysis demonstrated that the stromal expression of Osteopontin was an independent prognostic marker for overall and disease-free survival. Conclusion: The study identifies clinically relevant genomic alterations in the stroma of ICC, including candidates biomarkers for prognosis, supporting the idea that tumor stroma is an important factor for ICC onset and progression. (HEPATOLOGY 2013.).

[249]

TÍTULO / TITLE: - A sesquiterpene lactone antrocin from *Antrodia camphorata* negatively modulates JAK2/STAT3 signaling via microRNA let-7c and induces apoptosis in lung cancer cells.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt255](#)

AUTORES / AUTHORS: - Yeh CT; Huang WC; Rao YK; Ye M; Lee WH; Wang LS; Tzeng DT; Wu CH; Shieh YS; Huang CY; Chen YJ; Hsiao M; Wu AT; Yang Z; Tzeng YM

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Clinical Medicine, Taipei Medical University, Taipei.

RESUMEN / SUMMARY: - Lung cancer is the leading cause of cancer deaths worldwide and current therapies fail to treat this disease in majority of cases. *Antrodia camphorata* (AC), is a medicinal mushroom being widely used as food dietary supplement for cancer prevention. The sesquiterpene lactone antrocin is the most potent among more than one hundred secondary metabolites isolated from AC. However, the molecular mechanisms of antrocin-mediated anti-cancer effects remain unclear. In this study, we found that antrocin inhibited cell proliferation in two non-small cell lung cancer cells, namely H441 (wild-type EGFR, IC₅₀= 0.75μM) and H1975 (gefitinib-resistant mutant T790M, IC₅₀=0.83μM). Antrocin dose-dependently suppressed colony formation and induced apoptosis as evidenced by activated caspase-3 and increased Bax/Bcl2 ratio. Gene profiling studies indicated that antrocin downregulated JAK/STAT signaling pathway. We further demonstrated that antrocin suppressed both constitutively activated and IL-6-induced STAT3 phosphorylation and its subsequent nuclear translocation. Such inhibition is found to be achieved through the suppression of JAK2 and interaction between STAT3 and ERK. Additionally, antrocin increased microRNA let-7c expression and suppressed STAT signaling. The combination of antrocin and JAK2/STAT3 gene silencing significantly increased apoptosis in H441 cells. Such dual interruption of JAK2 and STAT3 pathways also induced downregulation of antiapoptotic protein mcl-1 and increased caspase-3 expression. In vivo, intraperitoneal administration of antrocin significantly suppressed the growth of lung cancer tumor xenografts. Our results indicate that antrocin may be a potential therapeutic agent for human lung cancer cells through constitutive inhibition of JAK2/STAT3 pathway.

[250]

TÍTULO / TITLE: - A chrysin derivative suppresses skin cancer growth by inhibiting cyclin-dependent kinases.

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

REVISTA / JOURNAL: - J Biol Chem. 2013 Jul 25.

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.464669](#)

AUTORES / AUTHORS: - Liu H; Liu K; Huang Z; Park CM; Thimmegowda NR; Jang JH; Ryoo IJ; He L; Kim SO; Oi N; Lee KW; Soung NK; Bode AM; Yang Y; Zhou X; Erikson RL; Ahn JS; Hwang J; Kim KE; Dong Z; Kim BY

INSTITUCIÓN / INSTITUTION: - The World Class Institute and Chemical Biology Research Center, Korea, Republic of;

RESUMEN / SUMMARY: - Chrysin (5,7-dihydroxyflavone), a natural flavonoid widely distributed in plants, reportedly has chemopreventive properties against various cancers. However, the anticancer activity of chrysin observed in in vivo studies has been disappointing. Here, we report that a chrysin derivative, referred to as compound 69407, more strongly inhibited EGF-induced neoplastic transformation of JB6 P+ cells compared to chrysin. It attenuated cell cycle progression of EGF-stimulated cells at the G1 phase and inhibited the G1/S transition. It caused loss of Rb phosphorylation at both Ser795 and Ser807/811, the preferred sites phosphorylated by Cdk4/6 and Cdk2, respectively. It also suppressed anchorage-dependent and -independent growth of A431 human epidermoid carcinoma cells. Compound 69407 reduced tumor growth in the A431 mouse xenograft model and Rb phosphorylation at Ser795 and Ser807/811. IP-kinase assay results showed that compound 69407 attenuated endogenous Cdk4 and Cdk2 kinase activities in EGF-stimulated JB6 P+ cells. Pulldown and in vitro kinase assay results indicated that compound 69407 directly binds with Cdk2 and Cdk4 in an ATP-independent manner and inhibited their kinase activities. A binding model between compound 69407 and a crystal structure of Cdk2 predicted that compound 69407 was located inside the Cdk2 allosteric binding site. The binding was further verified by a point mutation binding assay. Overall results indicated that compound 69407 is an ATP-noncompetitive Cdk inhibitor with anti-tumor effects, which acts by binding inside the Cdk2 allosteric pocket. The present study provides new insights for creating a general pharmacophore model to design and develop novel ATP-noncompetitive agents with chemopreventive or chemotherapeutic potency.

[251]

TÍTULO / TITLE: - Expression of nucleoside transporters (NT) and deoxycytidine kinase (dCK) proteins in muscle invasive urothelial carcinoma of the bladder (UCCB): correlation with pathologic response to neoadjuvant platinum/gemcitabine combination chemotherapy (NAC).

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

REVISTA / JOURNAL: - J Urol. 2013 Jul 9. pii: S0022-5347(13)04862-3. doi: 10.1016/j.juro.2013.07.006.

●● Enlace al texto completo (gratis o de pago) [1016/j.juro.2013.07.006](#)

AUTORES / AUTHORS: - North S; El-Gehani F; Santos C; Ghosh S; Lai R; Cass CE; Mackey JR

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada. Electronic address: scott.north@albertahealthservices.ca.

RESUMEN / SUMMARY: - **PURPOSE:** In pancreatic cancer, deoxycytidine kinase (dCK) and the human equilibrative nucleoside transporter 1 (hENT1) have been validated as predictive markers for benefit from gemcitabine therapy. Gemcitabine is used in combination with cisplatin or carboplatin as neoadjuvant chemotherapy (NAC) for muscle invasive urothelial cancer of the bladder (UCCB) prior to radical cystectomy and patients rendered disease free at time of surgery tend to have better outcomes. This trial examined if NT or dCK protein abundance in pre-chemotherapy biopsy specimens relate to response to NAC. **MATERIALS AND METHODS:** Sixty-two consecutive patients undergoing NAC with platinum/gemcitabine at a single institution were accrued. Initial transurethral resection of bladder tumor (TURBT) specimens as well as cystectomy specimens were collected and scored for NT and dCK expression. Pathologic response rates and survival data were collected. **RESULTS:** Seventeen of 62 (27%) patients achieved a complete pathologic response (pT0) to NAC. NT and dCK protein expression in TURBT specimens did not predict for pT0 status to NAC. Median overall survival has not been reached for the group achieving pT0 status and is 46 months for those with persistent cancer at time of definitive surgery (p=0.07). Median follow up for the cohort is 30 months. **CONCLUSIONS:** NT and dCK expression in TURBT samples do not predict for response to gemcitabine and platinum NAC. Patients should continue to be offered NAC prior to radical cystectomy based on clinical and pathological staging.

[252]

TÍTULO / TITLE: - BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-1391](https://doi.org/10.1158/1078-0432.CCR-13-1391)

AUTORES / AUTHORS: - Shen Y; Rehman FL; Feng Y; Boshuizen J; Bajrami I; Elliott R; Wang B; Lord CJ; Post LE; Ashworth A

INSTITUCIÓN / INSTITUTION: - Research, BioMarin Pharmaceutical Inc.

RESUMEN / SUMMARY: - **PURPOSE:** PARP1/2 inhibitors are a class of anticancer agents that target tumor-specific defects in DNA repair. Here, we describe BMN 673, a novel, highly potent PARP1/2 inhibitor with favorable metabolic stability, oral bioavailability and pharmacokinetic (PK) properties. **EXPERIMENTAL DESIGN:** Potency and selectivity of BMN 673 was

determined by biochemical assays. Anticancer activity either as a single-agent or in combination with other anti-tumor agents was evaluated both in vitro and in xenograft cancer models. RESULTS: BMN 673 is a potent PARP1/2 inhibitor (PARP1 IC50 = 0.57 nM), but does not inhibit other enzymes we have tested. BMN 673 exhibits selective anti-tumor cytotoxicity and elicits DNA repair biomarkers at much lower concentrations than earlier generation PARP1/2 inhibitors (such as olaparib, rucaparib and veliparib). In vitro, BMN 673 selectively targeted tumor cells with BRCA1, BRCA2 or PTEN gene defects with 20- to >200-fold greater potency than existing PARP1/2 inhibitors. BMN 673 is readily orally bioavailable, with >40% absolute oral bioavailability in rats when dosed in carboxymethyl cellulose. Oral administration of BMN 673 elicited remarkable anti-tumor activity in vivo; xenografted tumors that carry defects in DNA repair due to BRCA mutations or PTEN deficiency were profoundly sensitive to oral BMN 673 treatment at well tolerated doses in mice. Synergistic or additive anti-tumor effects were also found when BMN 673 was combined with temozolomide, SN38 or platinum drugs. CONCLUSION: BMN 673 is currently in early phase clinical development and represents a promising PARP1/2 inhibitor with potentially advantageous features in its drug class.

[253]

TÍTULO / TITLE: - Abnormal expression of insulin-like growth factor-I receptor in hepatoma tissue and its inhibition to promote apoptosis of tumor cells.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 25.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-0912-](#)

[Y](#)

AUTORES / AUTHORS: - Dong Z; Yao M; Wang L; Yan X; Gu X; Shi Y; Yao N; Qiu L; Wu W; Yao D

INSTITUCIÓN / INSTITUTION: - Department of Diagnostics, Affiliated Hospital of Nantong University, No. 20 West Temple Road, Nantong, 226001, China.

RESUMEN / SUMMARY: - Abnormal signaling of insulin-like growth factor I receptor (IGF-IR) is associated with hepatocellular carcinoma, but the underlying molecular mechanisms remain largely unknown. The objective of this study was to investigate IGF-IR's role as a signaling molecule, its pathological alteration in hepatoma tissues, and its effect on hepatoma cell proliferation when inhibited. As measured by immunohistochemical analysis, the incidence of hepatic IGF-IR expression in cancerous tissue was 80.0 % (24 of 30), which was significantly higher ($P < 0.05$) than 43.3 % (13 of 30) occurrence in the surrounding tissue and the nondetectable (0 of 30) frequency in the distal cancerous tissue. Hepatoma IGF-IR expression was correlated to the differentiation degree and not to the number or size of tumors, HBV infection, and AFP level. The in vitro IGF-IR expression in hepatoma cells was down-regulated significantly by picropodophyllin, a specific kinase inhibitor, in a time-

and dose-dependent manner. Cell proliferation was inhibited through typical mechanisms of promoting apoptosis and cell cycle arrest (G2/M phase). Up-regulation of IGF-IR in hepatocarcinogenesis suggests that the down-regulation of IGF-IR expression could be a specific molecular target for hepatoma cell proliferation.

[254]

TÍTULO / TITLE: - Why Denosumab Obtains a Survival Benefit over Zoledronic Acid in Bone Metastatic Lung Cancer Patients?

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug;8(8):e79. doi: 10.1097/JTO.0b013e318293e443.

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

[1097/JTO.0b013e318293e443](#)

AUTORES / AUTHORS: - Deiana L; Claps M; Berruti A

INSTITUCIÓN / INSTITUTION: - Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia Medical Oncology, Spedali Civili Hospital, Brescia, Italy.

[255]

TÍTULO / TITLE: - Inhibition of the Prohormone Convertase Subtilisin-Kexin Isoenzyme-1 Induces Apoptosis in Human Melanoma Cells.

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

REVISTA / JOURNAL: - J Invest Dermatol. 2013 Jun 27. doi: 10.1038/jid.2013.282.

●● Enlace al texto completo (gratis o de pago) [1038/jid.2013.282](#)

AUTORES / AUTHORS: - Weiss N; Stegemann A; Elsayed MA; Schallreuter KU; Luger TA; Loser K; Metze D; Weishaupt C; Bohm M

INSTITUCIÓN / INSTITUTION: - Laboratory for Neuroendocrinology of the Skin and Interdisciplinary Endocrinology, Department of Dermatology, University of Munster, Munster, Germany.

RESUMEN / SUMMARY: - Prohormone convertases (PCs) are endoproteases that process many substrates in addition to hormone precursors. Although overexpression of PCs is linked to carcinogenesis in some solid tumors, the role of subtilisin-kexin isoenzyme-1 (SKI-1) in this context is unknown. We show that SKI-1 is constitutively expressed in human pigment cells with higher SKI activity in seven out of eight melanoma cell lines compared with normal melanocytes. SKI-1 immunoreactivity is also detectable in tumor cells of melanoma metastases. Moreover, tissue samples of the latter display higher SKI-1 mRNA levels and activity than normal skin. From various stimuli tested, 12-O-tetradecanoylphorbol-13-acetate and tunicamycin affected SKI-1 expression. Importantly, SKI-1 inhibition by the cell-permeable enzyme inhibitor decanoyl-

RRL-chloromethylketone (dec-RRL-CMK) not only suppressed proliferation and metabolic activity of melanoma cells in vitro but also reduced tumor growth of melanoma cells injected intracutaneously into immunodeficient mice. Mechanistic studies revealed that dec-RRL-CMK induces classical apoptosis of melanoma cells in vitro and affects expression of several SKI-1 target genes including activating transcription factor 6 (ATF6). However, ATF6 gene silencing does not result in apoptosis of melanoma cells, suggesting that dec-RRL-CMK induces cell death in an ATF6-independent manner. Our findings encourage further studies on SKI-1 as a potential target for melanoma therapy. *Journal of Investigative Dermatology* advance online publication, 25 July 2013; doi:10.1038/jid.2013.282.

[256]

TÍTULO / TITLE: - Screening Bicyclic Peptide Libraries for Protein-Protein Interaction Inhibitors: Discovery of a Tumor Necrosis Factor-alpha Antagonist.

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

REVISTA / JOURNAL: - *J Am Chem Soc.* 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1021/ja405106u](#)

AUTORES / AUTHORS: - Lian W; Upadhyaya P; Rhodes CA; Liu Y; Pei D

INSTITUCIÓN / INSTITUTION: - Department of Chemistry and Biochemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States.

RESUMEN / SUMMARY: - Protein-protein interactions represent a new class of exciting but challenging drug targets, because their large, flat binding sites lack well-defined pockets for small molecules to bind. We report here a methodology for chemical synthesis and screening of large combinatorial libraries of bicyclic peptides displayed on rigid small-molecule scaffolds. With planar trimesic acid as the scaffold, the resulting bicyclic peptides are effective for binding to protein surfaces such as the interfaces of protein-protein interactions. Screening of a bicyclic peptide library against tumor necrosis factor-alpha (TNFalpha) identified a potent antagonist that inhibits the TNFalpha-TNFalpha receptor interaction and protects cells from TNFalpha-induced cell death. Bicyclic peptides of this type may provide a general solution for inhibition of protein-protein interactions.

[257]

TÍTULO / TITLE: - The prognostic significance of peroxisome proliferator-activated receptor beta expression in the vascular endothelial cells of colorectal cancer.

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

REVISTA / JOURNAL: - *J Gastroenterol.* 2013 Jul 3.

●● Enlace al texto completo (gratis o de pago) [1007/s00535-013-0845-](#)

[7](#)

AUTORES / AUTHORS: - Zhou J; Yang L; Li Y; Arbman G; Chen KL; Zhou B; Yu YY; Wang C; Mo XM; Lu Y; Zhou ZG; Sun XF

INSTITUCIÓN / INSTITUTION: - Institute of Digestive Surgery and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** Currently, little is known regarding the role of peroxisome proliferator-activated receptor-beta (PPAR beta) in the vascular endothelial cells (VECs) of colorectal cancers (CRCs). The aim of this study was to investigate the relationship of PPAR beta expression in the VECs of CRCs in terms of the prognosis and clinicopathological features of CRC patients. **DESIGN:** The expression and localization of PPAR beta in the primary cancers and the matched normal mucosal samples of 141 Swedish CRC patients were analyzed in terms of its correlation with clinicopathological features and the expression of angiogenesis-related genes. This study also included 92 Chinese CRC patients. **RESULTS:** PPAR beta was predominantly localized in the cytoplasm and was significantly downregulated in the VECs of CRC compared to that of the normal mucosa. The low expression levels of PPAR beta in the VECs of CRC were statistically correlated with enhanced differentiation, early staging and favorable overall survival and were associated with the increased expression of VEGF and D2-40. The patients exhibiting elevated expression of PPAR beta in CRC cells but reduced expression in VECs exhibited more favorable survival compared with the other patients, whereas the patients with reduced expression of PPAR beta in CRC cells but increased expression in VECs exhibited less favorable prognosis. **CONCLUSIONS:** PPAR beta might play a tumor suppressor role in CRC cells in contrast to a tumor promoter role in the VECs of CRCs.

[258]

TÍTULO / TITLE: - All-trans retinoic acid potentiates the chemotherapeutic effect of Cisplatin by inducing differentiation of tumor initiating cells in liver cancer.

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

REVISTA / JOURNAL: - J Hepatol. 2013 Jul 15. pii: S0168-8278(13)00456-X. doi: 10.1016/j.jhep.2013.07.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.jhep.2013.07.009](#)

AUTORES / AUTHORS: - Zhang Y; Guan DX; Shi J; Gao H; Li JJ; Zhao JS; Qiu L; Liu J; Li N; Guo WX; Xue J; Zhou FG; Wu MC; Wang HY; Xie D; Cheng SQ

INSTITUCIÓN / INSTITUTION: - Eastern Hepatobiliary Surgery Hospital, the Second Military Medical University, Shanghai, 200438, China.

RESUMEN / SUMMARY: - **BACKGROUND & AIMS:** Systemic chemotherapy serves as an adjuvant treatment for post-operation patients with hepatocellular carcinoma (HCC), and provides curative option for the patients with unresectable HCC. However, its efficiency is largely limited because of the high incidence of chemo-resistance. Increasing evidence has shown that tumor

initiating cells (TICs) not only have the ability to self-renew and drive the initiation and progression of cancer, but also exhibit greater resistance to conventional chemo- and radio-therapies than non-TICs. It was the aim of this study to investigate the effects of ATRA with and without cisplatin on TIC differentiation and apoptosis in human HCC. METHODS: In the present study, we evaluated the TICs of HCC cells differentiation induced by all-trans retinoic acid (ATRA), and developed a novel chemotherapeutic approach to HCC, by characterized the function of combinatorial treatment with cis-diammineplatinum(II) (Cisplatin) and ATRA in vitro and in vivo. RESULTS: ATRA effectively induced differentiation of TICs, which potentiated the cytotoxic effects of Cisplatin. The combinatorial treatment of ATRA acid and Cisplatin reduced protein kinase B (AKT) (Thr308) phosphorylation, and promoted apoptosis of HCC cells more significantly than treatment with Cisplatin alone. In addition, the combined treatment with the two drugs exerted stronger inhibition on either HCC cell migration in vitro or metastasis in vivo, when compared to the treatment with either drug alone. CONCLUSION: These results indicated that ATRA could significantly improve the effect of Cisplatin, which is at least partially attributed to ATRA-induced differentiation of HCC TICs, and the subsequent decrease in this chemo-resistant subpopulation. Key words: ATRA, Cisplatin, tumor initiating cell, differentiation, chemo-sensitivity, apoptosis, metastasis, hepatocellular carcinoma.

[259]

TÍTULO / TITLE: - Lung Adenocarcinoma Biomarker Incidence in Hispanic Versus Non-Hispanic White Patients.

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

REVISTA / JOURNAL: - Arch Pathol Lab Med. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [5858/arpa.2013-0225-](#)

[OA](#)

AUTORES / AUTHORS: - McQuitty E; Zhang W; Hendrickson H; Tio FO; Jagirdar J; Olsen R; Cagle P

INSTITUCIÓN / INSTITUTION: - From the Department of Pathology, University of Texas Health Sciences Center, San Antonio (Drs Zhang and Jagirdar); the Department of Anatomic and Clinical Pathology, South Texas Veterans Health Care System, San Antonio (Dr Tio); and the Department of Pathology and Genomic Medicine, Methodist Hospital, Houston, Texas (Drs McQuitty, Olsen, and Cagle and Ms Hendrickson). Dr McQuitty is now with the Department of Pathology and Immunology, Baylor College of Medicine, Houston.

RESUMEN / SUMMARY: - Context.-Lung cancer is the leading cause of cancer deaths in the United States and worldwide. Biomarker testing is critical to personalized therapy in lung adenocarcinoma and has been extensively investigated in non-Hispanic whites, Asians, and African Americans. However, little information addresses the underlying genetic changes in lung

adenocarcinoma among Hispanic patients in the United States. Objective.-To identify targetable biomarkers other than EGFR and EML4-ALK in Hispanic patients with lung adenocarcinoma. Design.-We tested DNA extracted from 85 lung adenocarcinoma specimens collected from 40 Hispanic and 43 non-Hispanic white patients for previously reported mutations in KRAS, MET, BRAF, mTOR, STAT3, JAK2, PIK3CA, AKT1 through AKT3, and PTEN with a custom Sequenom massARRAY assay (Sequenom, San Diego, California). Results.- Mutations in KRAS were identified in 11 cases (13%; 6 Hispanic [7%], 5 non-Hispanic white [6%]) and had no correlation with sex, age, or smoking history. Mutations in PIK3CA were identified in 2 of the 40 Hispanic patients (5%), including one patient (2.5%) with a concurrent KRAS mutation. The tumors were wild type for all other genes tested. Conclusions.-Targetable biomarkers other than EGFR and EML4-ALK were identified in 7 of the 40 Hispanic patients (18%) and 5 of the 43 non-Hispanic white patients (12%), suggesting a similar mutational frequency. Our highly multiplexed genotyping assay detected actionable mutations in 14% (12 of 83) more patients than would have been identified by EGFR and EML4-ALK testing alone.

[260]

TÍTULO / TITLE: - Covalent and allosteric inhibitors of the ATPase VCP/p97 induce cancer cell death.

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

REVISTA / JOURNAL: - Nat Chem Biol. 2013 Jul 28. doi: 10.1038/nchembio.1313.

●● [Enlace al texto completo \(gratis o de pago\) 1038/nchembio.1313](#)

AUTORES / AUTHORS: - Magnaghi P; D'Alessio R; Valsasina B; Avanzi N; Rizzi S; Asa D; Gasparri F; Cozzi L; Cucchi U; Orrenius C; Polucci P; Ballinari D; Perrera C; Leone A; Cervi G; Casale E; Xiao Y; Wong C; Anderson DJ; Galvani A; Donati D; O'Brien T; Jackson PK; Isacchi A

INSTITUCIÓN / INSTITUTION: - Business Unit Oncology, Nerviano Medical Sciences, Nerviano, Italy.

RESUMEN / SUMMARY: - VCP (also known as p97 or Cdc48p in yeast) is an AAA+ ATPase regulating endoplasmic reticulum-associated degradation. After high-throughput screening, we developed compounds that inhibit VCP via different mechanisms, including covalent modification of an active site cysteine and a new allosteric mechanism. Using photoaffinity labeling, structural analysis and mutagenesis, we mapped the binding site of allosteric inhibitors to a region spanning the D1 and D2 domains of adjacent protomers encompassing elements important for nucleotide-state sensing and ATP hydrolysis. These compounds induced an increased affinity for nucleotides. Interference with nucleotide turnover in individual subunits and distortion of interprotomer communication cooperated to impair VCP enzymatic activity. Chemical expansion of this allosteric class identified NMS-873, the most potent and specific VCP inhibitor described to date, which activated the unfolded protein

response, interfered with autophagy and induced cancer cell death. The consistent pattern of cancer cell killing by covalent and allosteric inhibitors provided critical validation of VCP as a cancer target.

[261]

TÍTULO / TITLE: - Up-regulation of DDX39 in Human Pancreatic Cancer Cells with Acquired Gemcitabine Resistance Compared to Gemcitabine-sensitive Parental Cells.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3133-6.

AUTORES / AUTHORS: - Kuramitsu Y; Suenaga S; Wang Y; Tokuda K; Kitagawa T; Tanaka T; Akada J; Maehara S; Maehara Y; Nakamura K

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Functional Proteomics, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. climates@yamaguchi-u.ac.jp.

RESUMEN / SUMMARY: - Intrinsic or acquired resistance of pancreatic cancer to gemcitabine (2'-deoxy-2'-difluorodeoxycytidine) is an important factor in the failure of gemcitabine treatment. Proteomic analysis of gemcitabine-sensitive KLM1 pancreatic cancer cells and -resistant KLM1-R cells identified heat-shock protein-27(HSP27) as a biomarker protein which is involved in gemcitabine resistance. However, a knock-down experiment showed that HSP27 was not the only protein implicated with gemcitabine-resistance. Finding further candidate proteins is necessary for achieving effective gemcitabine therapy for patients with pancreatic cancer. DDX39 is an Asp-Glu-Ala-Asp (DEAD)-box RNA helicase reported to be overexpressed in tumor cells, such as lung squamous cell cancer, gastrointestinal stromal tumor, urinary bladder cancer and malignant pleural mesothelioma. In urinary bladder cancer cells, overexpression of this protein is intimately bound with tumorigenesis and poor prognosis. In the present study, the expression of DDX39 in gemcitabine-sensitive KLM1 and -resistant KLM1-R cells was compared. It was found that DDX39 was significantly up-regulated in gemcitabine-resistant KLM1-R cells compared to sensitive KLM1 cells. The ratio of expression of DDX39 to that of actin was significantly up-regulated in KLM1-R cells compared to KLM1 cells ($p=0.0072$ by Student's t-test). These results suggest that DDX39 is a possible candidate biomarker for predicting the response of patients with pancreatic cancer to treatment with gemcitabine.

[262]

TÍTULO / TITLE: - Prostate apoptosis response-4 is involved in the apoptosis response to docetaxel in MCF-7 breast cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Aug;43(2):531-8. doi: 10.3892/ijo.2013.1983. Epub 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1983](https://doi.org/10.3892/ijo.2013.1983)

AUTORES / AUTHORS: - Pereira MC; de Bessa-Garcia SA; Burikhanov R; Pavanelli AC; Antunes L; Rangnekar VM; Nagai MA

INSTITUCIÓN / INSTITUTION: - Discipline of Oncology, Department of Radiology and Oncology, Faculty of Medicine, University of Sao Paulo, CEP 01246-903, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - Experimental evidence indicates that prostate apoptosis response-4 (Par-4, also known as PAWR) is a key regulator of cancer cell survival and may be a target for cancer-selective targeted therapeutics. Par-4 was first identified in prostate cancer cells undergoing apoptosis. Both intracellular and extracellular Par-4 have been implicated in apoptosis. Relatively little is known about the role of Par-4 in breast cancer cell apoptosis. In this study, we sought to investigate the effects of Par-4 expression on cell proliferation, apoptosis and drug sensitivity in breast cancer cells. MCF-7 cells were stably transfected with expression vectors for Par-4, or transiently transfected with siRNA for Par-4 knockdown. Cell proliferation assays were performed using MTT and apoptosis was evaluated using acridine orange staining, fluorescence microscopy and flow cytometry. Par-4 overexpression reduced MCF-7 proliferation rates. Conversely, Par-4 knockdown led to increased MCF-7 proliferation. Par-4 downregulation also led to increased BCL-2 and reduced BID expression. Par-4 overexpression did not affect the cell cycle profile. However, MCF-7 cells with increased Par-4 expression showed reduced ERK phosphorylation, suggesting that the inhibition of cell proliferation promoted by Par-4 may be mediated by the MAPK/ERK1/2 pathway. MCF-7 cells with increased Par-4 expression showed a marginal increase in early apoptotic cells. Importantly, we found that Par-4 expression modulates apoptosis in response to docetaxel in MCF7 breast cancer cells. Par-4 exerts growth inhibitory effects on breast cancer cells and chemosensitizes them to docetaxel.

[263]

TÍTULO / TITLE: - A Phase II Study of the Histone Deacetylase Inhibitor Panobinostat (LBH589) in Pretreated Patients with Small-Cell Lung Cancer.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug;8(8):1091-1094.

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

[1097/JTO.0b013e318293d88c](https://doi.org/10.1097/JTO.0b013e318293d88c)

AUTORES / AUTHORS: - de Marinis F; Atmaca A; Tiseo M; Giuffreda L; Rossi A; Gebbia V; Antonio CD; Zotto LD; Al-Batran SE; Marsoni S; Wolf M

INSTITUCIÓN / INSTITUTION: - *Department of Pulmonary-Oncology, San Camillo Hospital, Rome, Italy; daggerDepartment of Oncology and Hematology, Institute

of Clinical Research at Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; double daggerDepartment of Medical Oncology, University Hospital, Parma, Italy; section signDepartment of Medical Oncology, Molinette Hospital, Turin, Italy; ||Department of Medical Oncology, S. Giuseppe Moscati Hospital, Avellino, Italy; paragraph signDepartment of Medical Oncology, Maddalena Clinic, University of Palermo, Italy; #Southern Europe New Drugs Organization, Milan, Italy; and **Klinikum Kassel, Kassel, Germany.

RESUMEN / SUMMARY: - BACKGROUND:: In vitro data suggest that panobinostat (LBH589), a pan-deacetylase inhibitor, may add therapeutic benefit in the treatment of small-cell lung cancer (SCLC) with regression of tumors. METHODS:: This multicenter, nonrandomized phase 2 trial was designed to evaluate antitumor activity of LBH589 in patients with previously treated SCLC. Patients received LBH589 administered intravenously at a dose of 20 mg/mq (days 1-8) every 21 days. RESULTS:: A total of 21 patients with extensive- or limited-stage SCLC were enrolled. Patients received a median of two cycles (range, 1-6). LBH589 was well tolerated, and the most common toxicities were grade 1 to 2 gastrointestinal disorders (nausea 38%, diarrhea 24%, vomiting 19%), grade 1 to 2 thrombocytopenia (14.3%). Of 19 patients evaluable for efficacy, two cases showed shrinkages more than 30% at first assessment, with time to progression of 14 and 21 weeks, respectively, and there were three long disease stabilizations of 12, 10, and 13 weeks. The study was prematurely closed because of a lack of activity. CONCLUSION:: This is the first report of a pan-deacetylase inhibitor inducing tumor shrinkage and sustained stable disease in SCLC. We believe that although the trial was prematurely discontinued, modest clinical activity of LBH589 combined with a favorable safety profile in pretreated SCLC patients was observed, which warrants further exploration of the potential contribution of LBH589 in other trials.

[264]

TÍTULO / TITLE: - Salvianolic Acid B Induces Apoptosis in Human Glioma U87 Cells Through p38-Mediated ROS Generation.

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

REVISTA / JOURNAL: - Cell Mol Neurobiol. 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [1007/s10571-013-9958-](#)

[Z](#)

AUTORES / AUTHORS: - Wang ZS; Luo P; Dai SH; Liu ZB; Zheng XR; Chen T

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, First Affiliated Hospital of Bengbu Medical College, Bengbu, 233004, Anhui, China, bengyiwangzishu@163.com.

RESUMEN / SUMMARY: - Salvianolic acid B (SalB), the main water-soluble bioactive compounds isolated from the traditional Chinese medical herb Danshen, has been shown to exert anti-cancer effect in several cancer cell

lines. The aim of our study was to investigate the potential anti-cancer effect of SalB in human glioma U87 cells. We found that treatment with SalB significantly decreased cell viability of U87 cells in a dose- and time-dependent manner. SalB also enhanced the intracellular ROS generation and induced apoptotic cell death in U87 cells. Western blot analysis suggested that SalB increased the phosphorylation of p38 MAPK and p53 in a dose-dependent manner. Moreover, blocking p38 activation by specific inhibitor SB203580 or p38 specific siRNA partly reversed the anti-proliferative and pro-apoptotic effects, and ROS production induced by SalB treatment. The anti-tumor activity of SalB in vivo was also demonstrated in U87 xenograft glioma model. All of these findings extended the anti-cancer effect of SalB in human glioma cell lines, and suggested that these inhibitory effects of SalB on U87 glioma cell growth might be associated with p38 activation mediated ROS generation. Thus, SalB might be concerned as an effective and safe natural anticancer agent for glioma prevention and treatment.

[265]

TÍTULO / TITLE: - Autophagy stimulates apoptosis in HER2-overexpressing breast cancers treated by lapatinib.

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

REVISTA / JOURNAL: - J Cell Biochem. 2013 Jun 21. doi: 10.1002/jcb.24611.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24611](#)

AUTORES / AUTHORS: - Zhu X; Wu L; Qiao H; Han T; Chen S; Liu X; Jiang R; Wei Y; Feng D; Zhang Y; Ma Y; Zhang S; Zhang J

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Chemistry, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shaanxi, 710032, China.

RESUMEN / SUMMARY: - HER2-overexpressing breast cancers often show hyperactivation of the HER2/AKT/mTOR signaling pathway. Lapatinib is an oral dual tyrosine kinase inhibitor(TKI) that targets both EGFR and HER2 to inhibit the proliferation of breast cancer cells. However, it is obscure whether and how lapatinib could induce autophagy in breast cancer cells, an important cell response with drug treatment. In this study, we investigated the apoptosis and the autophagy in the HER2-overexpressing breast cancer cells BT474 and AU565 treated with lapatinib, and further examined their relationship. Lapatinib inhibited the proliferation and the rate of DNA synthesis in HER2-positive cells, as observed by MTT, colony formation and EDU assays. Lapatinib not only induced apoptosis accompanied by an increased expression of cleaved Caspase-3 and cleaved PARP, but it also induced autophagy in vitro, as confirmed by electron microscopy (EM), acridine orange (AO) staining and LC3-II expression. Meanwhile, lapatinib inhibited the phosphorylation of HER2, AKT, mTOR and p70S6K, whereas that of AMPK was activated. When the cells were pre-incubated with 3-Methyladenine (3-MA), the specific autophagy inhibitor, the growth inhibitory ratio and apoptosis rate were frustrated, whereas colony

formation and DNA synthesis ability were encouraged. In addition, 3-MA application could up-regulate Caspase-3 and PARP expression, compared with the treatment with lapatinib alone. The addition of 3-MA could attenuate the inhibitory role on HER2/AKT/mTOR pathway and the active role on AMPK that was raised by lapatinib. Therefore, lapatinib simultaneously induced both apoptosis and autophagy in the BT474 and AU565 cells, and in these settings, autophagy facilitates apoptosis. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[266]

TÍTULO / TITLE: - Impact of P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) gene dosage on plasma pharmacokinetics and brain accumulation of dasatinib, sorafenib and sunitinib.

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

REVISTA / JOURNAL: - J Pharmacol Exp Ther. 2013 Jul 10.

●● [Enlace al texto completo \(gratis o de pago\) 1124/jpet.113.205583](#)

AUTORES / AUTHORS: - Tang SC; de Vries N; Sparidans RW; Wagenaar E; Beijnen JH; Schinkel AH

INSTITUCIÓN / INSTITUTION: - 1 The Netherlands Cancer Institute;

RESUMEN / SUMMARY: - Low brain accumulation of anticancer drugs due to efflux transporters may limit chemotherapeutic efficacy, necessitating better understanding of the underlying mechanisms. P-glycoprotein (Abcb1a/1b) and breast cancer resistance protein (Abcg2) combination knockout mice often display disproportionately increased brain accumulation of shared drug substrates compared to single transporter knockout mice. Recently developed pharmacokinetic models could explain this phenomenon. To experimentally test these models and their wider relevance for tyrosine kinase inhibitors (TKIs) and other drugs, we selected dasatinib, sorafenib and sunitinib because of their divergent oral availability and brain accumulation profiles: brain accumulation of dasatinib is mainly restricted by Abcb1, that of sorafenib mainly by Abcg2, and that of sunitinib equally by Abcb1 and Abcg2. We analyzed the effect of halving the efflux activity of these transporters at the blood-brain barrier (BBB) by generating heterozygous Abcb1a/1b;Abcg2 knockout mice, and testing plasma and brain levels of the drugs after oral administration at 10 mg/kg. RT-PCR analysis confirmed ~2-fold decreased expression of both transporters in brain. Interestingly, whereas complete knockout of the transporters caused 24- to 36-fold increases in brain accumulation of the drugs, the heterozygous mice only displayed 1.6- to 1.9-fold increases of brain accumulation relative to wild-type mice. These results are well in line with the predictions of the pharmacokinetic models, and provide strong support for their validity for a wider range of drugs. Moreover, retrospective analysis of fetal accumulation of drugs across the placenta in Abcb1a/1b heterozygous knockout pups suggests that these models equally apply to the maternal-fetal barrier.

[267]

TÍTULO / TITLE: - Lenalidomide: A Review of its Use in Patients with Transfusion-Dependent Anaemia due to Low- or Intermediate-1-Risk Myelodysplastic Syndrome Associated with 5q Chromosome Deletion.

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

REVISTA / JOURNAL: - Drugs. 2013 Jul;73(11):1183-96. doi: 10.1007/s40265-013-0071-x.

●● Enlace al texto completo (gratis o de pago) [1007/s40265-013-0071-](#)

[X](#)

AUTORES / AUTHORS: - Syed YY; Scott LJ

INSTITUCIÓN / INSTITUTION: - Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore, 0754, Auckland, New Zealand, demail@adis.com.

RESUMEN / SUMMARY: - Lenalidomide (Revlimid®), a thalidomide analogue, is an orally administered second generation immunomodulator with anti-angiogenic, antineoplastic, anti-inflammatory and pro-erythropoietic properties. It is approved for the treatment of patients with transfusion-dependent anaemia due to International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome (MDS) associated with either chromosome 5q deletion [del(5q)] with or without additional cytogenetic abnormalities (US, Japan and Switzerland etc.), or with an isolated del(5q) cytogenetic abnormality when other therapeutic options are insufficient or inadequate (EU) [featured indication]. In a randomized, double-blind, multicentre, registrational trial (MDS-004; n = 205) in this patient population, a significantly higher proportion of lenalidomide recipients than placebo recipients achieved red blood cell transfusion independence for ≥ 26 consecutive weeks (primary endpoint for efficacy) and cytogenetic responses. The erythroid response to lenalidomide was accompanied by an increase in the haemoglobin levels. These efficacy outcomes are generally consistent with those seen in an earlier noncomparative registrational trial (MDS-003; n = 148). In MDS-004, lenalidomide also significantly improved health-related quality of life compared with placebo at 12 weeks. Retrospective analyses that compared outcomes between lenalidomide-treated patients with low- or intermediate-1-risk del(5q) MDS and multicentre registry cohorts showed that lenalidomide treatment did not appear to increase the risk of progression to acute myeloid leukaemia. Lenalidomide had a manageable safety profile in the registrational trials, with ≤ 20 % of patients discontinuing treatment because of adverse events. The most common adverse events (incidence ≥ 20 %) occurring in lenalidomide recipients were thrombocytopenia and neutropenia, which were generally managed by dosage reductions and/or interruptions, and/or pharmacotherapy. Thus, lenalidomide is a useful option for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk del(5q) MDS, with or without additional cytogenetic abnormalities.

[268]

TÍTULO / TITLE: - Targeted drug delivery and cross-linking induced apoptosis with anti-CD37 based dual-ligand immunoliposomes in B chronic lymphocytic leukemia cells.

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

REVISTA / JOURNAL: - Biomaterials. 2013 Aug;34(26):6185-93. doi: 10.1016/j.biomaterials.2013.04.063. Epub 2013 May 28.

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

1016/j.biomaterials.2013.04.063

AUTORES / AUTHORS: - Yu B; Mao Y; Yuan Y; Yue C; Wang X; Mo X; Jarjoura D; Paulaitis ME; Lee RJ; Byrd JC; Lee LJ; Muthusamy N

INSTITUCIÓN / INSTITUTION: - Department of Chemical and Biomolecular Engineering, The Ohio State University, Columbus, OH, USA.

RESUMEN / SUMMARY: - Despite advances in chemo and immunotherapeutic agents for B chronic lymphocytic leukemia (B-CLL), the undesirable adverse side effects due to non-specific cellular uptake remain to be addressed. We identified anti-CD37 monoclonal antibody immunoliposomes (ILs) as vehicles for targeted delivery to B chronic lymphocytic leukemia cells. To achieve maximal benefits for all patients, a new strategy of dual-ligand immunoliposomes (dILs) was developed. A combinatorial antibody microarray technology was adapted to quickly identify optimal antibody combinations for individual patient cells. For proof-of-concept, a B-cell specific antibody, either anti-CD19 or anti-CD20, was combined with anti-CD37 to construct dILs with enhanced selectivity and efficacy. Consistent with data from the antibody microarray, these dILs provided highly specific targeting to both leukemia cell lines and B-CLL patient cells. Compared with the single antibody ILs, the anti-CD19/CD37 dILs clearly demonstrated superior delivery efficiency and apoptosis induction to B-CLL patient cells, whereas the anti-CD20/anti-CD37 dILs were found to be the most efficient for delivery to leukemia cell lines. In addition, it was observed that anti-CD37 ILs without payload drug mediated effective CD37 cross-linking and induced potent apoptosis induction. The anti-CD19/CD20 dILs showed the improved cell apoptosis induction compared to either anti-CD19 ILs or anti-CD20 ILs. Our findings suggest that the dual-ligand ILs may provide a preferred strategy of personalized nanomedicine for the treatment of B-cell malignancies.

[269]

TÍTULO / TITLE: - ANCCA Protein Expression is a Novel Independent Poor Prognostic Marker in Surgically Resected Lung Adenocarcinoma.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 18.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3027-](https://doi.org/10.1245/s10434-013-3027-1)

[1](#)

AUTORES / AUTHORS: - Zhang Y; Sun Y; Li Y; Fang Z; Wang R; Pan Y; Hu H; Luo X; Ye T; Li H; Wang L; Chen H; Ji H

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China.

RESUMEN / SUMMARY: - BACKGROUND: AAA+ nuclear coregulator cancer associated (ANCCA) is found to be overexpressed in various cancer types and could play a role in common and fundamental cellular processes. A recent study suggested that ANCCA was a likely driver whose expression explained the behavior of differentially expressed proliferation-related genes in lung adenocarcinoma. However, protein expression of ANCCA in lung adenocarcinoma and its association with clinicopathologic parameters and commonly reported driver mutations remains unexplored. METHODS: ANCCA expression was evaluated by immunohistochemistry in 143 surgically resected lung adenocarcinomas and was correlated with clinicopathologic and molecular variables including adenocarcinoma histologic subtypes, tumor, node, metastasis status, relapse-free survival, overall survival, EGFR mutations, KRAS mutations, HER2 mutations and ALK fusions. RESULTS: Positive ANCCA expression was significantly associated with male sex, smokers, poorly differentiated tumors, nonlepidic predominant subtype, more advanced T stage, lymph nodal metastasis and late disease stage. Cox multivariate analysis revealed that ANCCA-positive expression was an independent predictor of worse relapse-free survival [hazard ratio (HR) 1.736, 95 % confidence interval (CI) 1.075-2.804; P = .024] and overall survival (HR 7.758, 95 % CI 2.955-20.370; P < .001). The addition of ANCCA protein expression to the prognostic model using pathologic stage markedly improved the prognostic accuracy; the concordance index increased from .692 to .788, and the Akaike information criterion decreased from 354.20 to 336.11. CONCLUSIONS: We have identified ANCCA protein expression as a novel independent poor prognostic indicator in lung adenocarcinoma. Prospective studies are warranted to validate its potential prognostic value in combination with the current staging system.

[270]

TÍTULO / TITLE: - MicroRNA-7 downregulates XIAP expression to suppress cell growth and promote apoptosis in cervical cancer cells.

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

REVISTA / JOURNAL: - FEBS Lett. 2013 Jul 11;587(14):2247-53. doi: 10.1016/j.febslet.2013.05.054. Epub 2013 Jun 4.

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

[1016/j.febslet.2013.05.054](https://doi.org/10.1016/j.febslet.2013.05.054)

AUTORES / AUTHORS: - Liu S; Zhang P; Chen Z; Liu M; Li X; Tang H

INSTITUCIÓN / INSTITUTION: - Tianjin Life Science Research Center and Basic Medical School, Tianjin Medical University, Tianjin, China.

RESUMEN / SUMMARY: - Our study demonstrated the functions of microRNA-7 (miR-7) in cervical cancer. The overexpression of miR-7 in the cervical cancer cell lines HeLa and C-33^a suppressed cell viability and promoted cell apoptosis, whereas the inhibition of miR-7 had opposite effects. Furthermore, an oncogene, X-linked inhibitor of apoptosis protein (XIAP), was identified as a new target of miR-7, and the ectopic expression of XIAP rescued the effects induced by miR-7 in HeLa and C-33^a cells. These results indicate that miR-7 targeted and downregulated the oncogene XIAP to regulate the effect of miR-7 on apoptosis and malignant behaviors of HeLa and C-33^a cells.

[271]

TÍTULO / TITLE: - Autophagy enhances antitumor immune responses induced by irradiated hepatocellular carcinoma cells engineered to express hepatitis B virus X protein.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Aug;30(2):993-9. doi: 10.3892/or.2013.2531. Epub 2013 Jun 10.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2531](#)

AUTORES / AUTHORS: - Yan Y; Liu N; Lu L; Zang CM; Shao B; Li Y; Wen Y; Wei Y; Cheng P

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610041, P.R. China.

RESUMEN / SUMMARY: - Hepatitis B virus X protein (HBx) plays a critical role in malignancy transformation of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). HBx sequence has been mapped with multi-epitopes which can elicit robust specific cytolytic T lymphocyte (CTL) responses. In our previous study, we developed an adenoviral vaccine against HBx oncoproteins to prevent growth of HBV-associated HCC. However, due to the weak immunogenicity of tumor antigen and pre-existing virus-neutralizing antibodies to the vaccine carrier preventing the vector from transducing target cells, the development of novel methods to enhance antigen presentation is urgently required. In the present study, we developed an adenoviral-mediated genetic engineering of hepatoma cell vaccine to express HBx and to evaluate if the novel vaccine could elicit specific immune responses. Our data showed that the irradiated tumor cells engineered to express HBx could significantly induce antitumor immune responses in vivo. The novel vaccine could induce a specific CTL response to recognize and lyse HBx-positive hepatoma cells in vitro. Both CD8⁺ T and CD4⁺ T lymphocytes are involved in the antitumor immune response induced by the novel vaccine. Furthermore, numerous autophagosomes and autolysosomes were found in the irradiated tumor cells

engineered to express HBx. The results demonstrated that the irradiated HBx-modified tumor cell vaccine was a potent and promising therapeutic agent against HBx-positive HCC via induction of autophagy-enhanced CD8+ T and CD4+ T lymphocyte-mediated antitumor immune responses. The present findings have implications for the development of clinical immunotherapy against HBV-associated HCC.

[272]

TÍTULO / TITLE: - The phosphatidylinositol-3-kinase inhibitor NVP-BKM120 overcomes resistance signals derived from microenvironment by regulating the Akt/FoxO3a/Bim axis in chronic lymphocytic leukemia cells.

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

REVISTA / JOURNAL: - Haematologica. 2013 Jul 12.

- Enlace al texto completo (gratis o de pago)

[3324/haematol.2013.088849](#)

AUTORES / AUTHORS: - Rosich L; Saborit-Villarroya I; Lopez-Guerra M; Xargay-Torrent S; Montraveta A; Aymerich M; Villamor N; Campo E; Perez-Galan P; Roue G; Colomer D

INSTITUCIÓN / INSTITUTION: - España;

RESUMEN / SUMMARY: - Phosphatidylinositol-3-kinase pathway is constitutively activated in chronic lymphocytic leukemia mainly due to microenvironment signals, including stromal cell interaction and CXCR4 and B-cell receptor activation. Because of the importance of phosphatidylinositol-3-kinase signaling in chronic lymphocytic leukemia, we investigated the activity of the NVP-BKM120, an orally available pan class I phosphatidylinositol-3-kinase inhibitor. Sensitivity to NVP-BKM120 was analyzed in chronic lymphocytic leukemia primary samples in the context of B-cell receptor and microenvironment stimulation. NVP-BKM120 promoted mitochondrial apoptosis in most primary cells independently of common prognostic markers. NVP-BKM120 activity induced the blockage of phosphatidylinositol-3-kinase signalling, decreased Akt and FoxO3a phosphorylation leading to concomitant Mcl-1 downregulation and Bim induction. Accordingly, selective knockdown of BIM rescued cells from NVP-BKM120-induced apoptosis, while the kinase inhibitor synergistically enhanced the apoptosis induced by the BH3-mimetic ABT-263. We also found NVP-BKM120 to inhibit B-cell receptor- and stroma-dependent Akt pathway activation, thus sensitizing CLL cells to bendamustine and fludarabine. Furthermore, NVP-BKM120 downregulated secretion of chemokines after B-cell receptor stimulation and inhibited cell chemotaxis and actin polymerization upon CXCR4 triggering by CXCL12. Our findings establish that NVP-BKM120 effectively inhibits the phosphatidylinositol-3-kinase signalling pathway and disturbs the protective effect of the tumor microenvironment with the subsequent apoptosis induction through the Akt/FoxO3a/Bim axis. We provide

here a strong rationale for undertaking clinical trials of NVP-BKM120 in chronic lymphocytic leukemia patients alone or in combination therapies.

[273]

TÍTULO / TITLE: - Cost-effectiveness of full coverage of aromatase inhibitors for Medicare beneficiaries with early breast cancer.

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

REVISTA / JOURNAL: - Cancer. 2013 Jul 1;119(13):2494-502. doi: 10.1002/cncr.28084. Epub 2013 Apr 23.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28084](#)

AUTORES / AUTHORS: - Ito K; Elkin E; Blinder V; Keating N; Choudhry N

INSTITUCIÓN / INSTITUTION: - Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. kito@une.edu

RESUMEN / SUMMARY: - BACKGROUND: Rates of nonadherence to aromatase inhibitors (AIs) among Medicare beneficiaries with hormone receptor-positive early breast cancer are high. Out-of-pocket drug costs appear to be an important contributor to this and may be addressed by eliminating copayments and other forms of patient cost sharing. The authors estimated the incremental cost-effectiveness of providing Medicare beneficiaries with full prescription coverage for AIs compared with usual prescription coverage under the Medicare Part D program. METHODS: A Markov state-transition model was developed to simulate AI use and disease progression in a hypothetical cohort of postmenopausal Medicare beneficiaries with hormone receptor-positive early breast cancer. The analysis was conducted from the societal perspective and considered a lifetime horizon. The main outcome was an incremental cost-effectiveness ratio, which was measured as the cost per quality-adjusted life-year (QALY) gained. RESULTS: For patients receiving usual prescription coverage, average quality-adjusted survival was 11.35 QALYs, and lifetime costs were \$83,002. For patients receiving full prescription coverage, average quality-adjusted survival was 11.38 QALYs, and lifetime costs were \$82,728. Compared with usual prescription coverage, full prescription coverage would result in greater quality-adjusted survival (0.03 QALYs) and less resource use (\$275) per beneficiary. From the perspective of Medicare, full prescription coverage was cost-effective (incremental cost-effectiveness ratio, \$15,128 per QALY gained) but not cost saving. CONCLUSIONS: Providing full prescription coverage for AIs to Medicare beneficiaries with hormone receptor-positive early breast cancer would both improve health outcomes and save money from the societal perspective.

[274]

TÍTULO / TITLE: - Targeting acute myeloid leukemia with a proapoptotic peptide conjugated to a toll-like receptor 2-mediated cell-penetrating peptide.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 13. doi: 10.1002/ijc.28382.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28382](#)

AUTORES / AUTHORS: - Li K; Lv XX; Hua F; Lin H; Sun W; Cao WB; Fu XM; Xie J; Yu JJ; Li Z; Liu H; Han MZ; Hu ZW

INSTITUCIÓN / INSTITUTION: - Molecular Immunology and Pharmacology Group, State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100050, P.R. China.

RESUMEN / SUMMARY: - Cell-penetrating peptides provide a unique platform to create a new generation of cancer therapeutics with enhanced efficacy and diminished toxicity. In this study, enhanced expression of toll like receptor 2 (TLR2) was observed in acute myeloid leukemia (AML) cells. Screening of a phage display peptide library using Bio-panning and Rapid Analysis of Selective Interactive Ligands (BRASIL) identified a TLR2-binding peptide motif, Pep2. We show that the TLR2-binding peptide motif targeted and penetrated into leukemia cells in a TLR2-dependent manner. Moreover, a synthetic, chimeric peptide composed of the TLR2-binding motif linked to a programmed cell death-inducing sequence, D(KLAKLAK)2, induced apoptosis in AML cells with high TLR2 expression (TLR2^{high}) but not in chronic myeloid leukemia (CML) cells with low TLR2 expression (TLR2^{low}). The anti-leukemia activity of this chimeric peptide was confirmed in leukemia patient samples and an animal model of myeloid leukemia, as the development of leukemia was significantly delayed in mice with TLR2^{high} AML compared to TLR2^{low} CML NOD/SCID mice. TUNEL assays on bone marrow tissue slices revealed that the chimerical peptide induced leukemia cell apoptosis in a TLR2-dependent manner. Together, our findings indicate that TLR2 is a potential therapeutic target for the prevention and treatment of AML, and the prototype, Pep2-D(KLAKLAK)2, is a promising drug candidate in this setting. © 2013 Wiley Periodicals, Inc.

[275]

TÍTULO / TITLE: - EGFR-SGLT1 interaction does not respond to EGFR modulators, but inhibition of SGLT1 sensitizes prostate cancer cells to EGFR tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Prostate. 2013 Jun 14. doi: 10.1002/pros.22692.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22692](#)

AUTORES / AUTHORS: - Ren J; Bollu LR; Su F; Gao G; Xu L; Huang WC; Hung MC; Weihua Z

INSTITUCIÓN / INSTITUTION: - Department of Biology and Biochemistry, College of Natural Sciences and Mathematics, University of Houston, Houston, Texas.

RESUMEN / SUMMARY: - BACKGROUND: Overexpression of epidermal growth factor receptor (EGFR) is associated with poor prognosis in malignant tumors. Sodium/glucose co-transporter 1 (SGLT1) is an active glucose transporter that is overexpressed in many cancers including prostate cancer. Previously, we found that EGFR interacts with and stabilizes SGLT1 in cancer cells. METHODS: In this study, we determined the micro-domain of EGFR that is required for its interaction with SGLT1 and the effects of activation/inactivation of EGFR on EGFR-SGLT1 interaction, measured the expression of EGFR and SGLT1 in prostate cancer tissues, and tested the effect of inhibition of SGLT1 on the sensitivity of prostate cancer cells to EGFR tyrosine inhibitors. RESULTS: We found that the autophosphorylation region (978-1210 amino acids) of EGFR was required for its sufficient interaction with SGLT1 and that this interaction was independent of EGFR's tyrosine kinase activity. Most importantly, the EGFR-SGLT1 interaction does not respond to EGFR tyrosine kinase modulators (EGF and tyrosine kinase inhibitors). EGFR and SGLT1 co-localized in prostate cancer tissues, and inhibition of SGLT1 by a SGLT1 inhibitor (Phlorizin) sensitized prostate cancer cells to EGFR inhibitors (Gefitinib and Erlotinib). CONCLUSION: These data suggest that EGFR in cancer cells can exist as either a tyrosine kinase modulator responsive status or an irresponsive status. SGLT1 is a protein involved in EGFR's functions that are irresponsive to EGFR tyrosine kinase inhibitors and, therefore, the EGFR-SGLT1 interaction might be a novel target for prostate cancer therapy. Prostate Published 2013 Wiley Periodicals, Inc. This article is a U.S. Government work and is in the public domain in the USA.

[276]

TÍTULO / TITLE: - Epigenetics in clinical practice: the examples of azacitidine and decitabine in myelodysplasia and acute myeloid leukemia.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jun 12. doi: 10.1038/leu.2013.173.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.173](#)

AUTORES / AUTHORS: - Estey EH

INSTITUCIÓN / INSTITUTION: - Division of Hematology, University of Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA, USA.

RESUMEN / SUMMARY: - Randomized trials have clearly demonstrated that the hypomethylating agents azacitidine and decitabine are more effective than 'best supportive care' (BSC) in reducing transfusion frequency in 'low-risk' myelodysplasia (MDS) and in prolonging survival compared with BSC or low-dose ara-C in 'high-risk' MDS or acute myeloid leukemia (AML) with 21-30% blasts. They also appear equivalent to conventional induction chemotherapy in AML with >20% blasts and as conditioning regimens before allogeneic transplant (hematopoietic cell transplant, HCT) in MDS. Although azacitidine or

decitabine are thus the standard to which newer therapies should be compared, here we discuss whether the improvement they afford in overall survival is sufficient to warrant a designation as a standard in treating individual patients. We also discuss pre- and post-treatment covariates, including assays of methylation to predict response, different schedules of administration, combinations with other active agents and use in settings other than active disease, in particular post HCT. We note that rational development of this class of drugs awaits delineation of how much of their undoubted effect in fact results from hypomethylation and reactivation of gene expression. Leukemia advance online publication, 23 July 2013; doi:10.1038/leu.2013.173.

[277]

TÍTULO / TITLE: - Pretreatment Expression of 13 Molecular Markers as a Predictor of Tumor Responses After Neoadjuvant Chemoradiation in Rectal Cancer.

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

REVISTA / JOURNAL: - Ann Surg. 2013 Jun 19.

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

[1097/SLA.0b013e31829b3916](#)

AUTORES / AUTHORS: - Huh JW; Lee JH; Kim HR

INSTITUCIÓN / INSTITUTION: - *Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea daggerDepartment of Pathology; and double daggerDepartment of Surgery Chonnam National University Hwasun Hospital and Medical School, Gwangju, Korea.

RESUMEN / SUMMARY: - **OBJECTIVE::** This study evaluated the predictive value of a number of tissue biomarkers, including proliferating cell nuclear antigen, survivin, thymidine phosphorylase, thymidylate synthase, bax, p53, nuclear factor-kappa B, vascular endothelial growth factor, matrix metalloproteinase-2, matrix metalloproteinase-9, CD133, CD44, and cyclooxygenase-2 with regard to preoperative chemoradiation in rectal cancer. **BACKGROUND::** The ability to predict tumor response before treatment may significantly impact the selection of patients for preoperative chemoradiation therapy for rectal cancer. However, no definite predictive marker is known. **METHODS::** Pretreatment biopsies from 123 patients who underwent preoperative chemoradiation were included. The mRNA levels of 13 biomarkers were analyzed by reverse transcriptase-polymerase chain reaction, with normalization relative to glyceraldehydes 3-phosphate dehydrogenase. Response to treatment was assessed by a 4-point tumor regression grade scale based on the ratio of fibrosis to residual cancer. **RESULTS::** Among the 13 markers, no significant correlations in terms of T downstaging, N downstaging, and tumor-node-metastasis downstaging were observed. On multiple logistic regression analysis, only CD44 expression was found to be significant independent predictive factors for tumor regression grade response [odds ratio, 4.694 (1.155, 17.741), P = 0.030]. CD44 mRNA

expression was significantly associated with expressions of the remaining 12 markers (all $P < 0.05$). Among the 118 patients receiving radical resection, proliferating cell nuclear antigen was the only independent factor to predict pathologic node negative status [odds ratio, 4.328 (1.078, 12.536), $P = 0.037$]. CONCLUSIONS:: Elevated CD44 mRNA levels in pretreatment biopsies might be predictive of poor tumor regression after preoperative chemoradiation in rectal cancer. Moreover, the proliferating cell nuclear antigen mRNA level might be predictive of nodal regression.

[278]

TÍTULO / TITLE: - Resveratrol regulates the cell viability promoted by 17beta-estradiol or bisphenol A via down-regulation of the cross-talk between estrogen receptor alpha and insulin growth factor-1 receptor in BG-1 ovarian cancer cells.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Jun 27;59C:373-379. doi: 10.1016/j.fct.2013.06.029.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.06.029](#)

AUTORES / AUTHORS: - Kang NH; Hwang KA; Lee HR; Choi DW; Choi KC

INSTITUCIÓN / INSTITUTION: - Laboratory of Veterinary Biochemistry and Immunology, College of Veterinary Medicine, Chungbuk National University, Cheongju, Chungbuk 361-763, Republic of Korea; Research and Innovation Team, Dr. Chung's Food Co., Ltd., Cheongju, Chungbuk 361-782, Republic of Korea.

RESUMEN / SUMMARY: - Endocrine disrupting chemicals (EDCs) and estrogens appear to promote development of estrogen-dependent cancers, including breast and ovarian carcinomas. In this study, we evaluated the cell viability effect of BPA on BG-1 human ovarian cancer cells, along with the growth inhibitory effect of resveratrol (trans-3,4,5-trihydroxystilbene; RES), a naturally occurring phytoestrogen. In addition, we investigated the underlying mechanism(s) of BPA and RES in regulating the interaction between estrogen receptor alpha (ERalpha) and insulin-like growth factor-1 receptor (IGF-1R) signals, a non-genomic pathway induced by 17beta-estradiol (E2). BPA induced a significant increase in BG-1 cell growth and up-regulated mRNA levels of ERalpha and IGF-1R. In parallel with its mRNA level, the protein expression of ERalpha was induced, and phosphorylated insulin receptor substrate-1 (p-IRS-1), phosphorylated Akt1/2/3, and cyclin D1 were increased by BPA or E2. However, RES effectively reversed the BG-1 cell proliferation induced by E2 or BPA by inversely down-regulating the expressions of ERalpha, IGF-1R, p-IRS-1, and p-Akt1/2/3, and cyclin D1 at both transcriptional and translational levels. Taken together, these results suggest that RES is a novel candidate for prevention of tumor progression caused by EDCs, including BPA via effective inhibition of the cross-talk of ERalpha and IGF-1R signaling pathways.

[279]

TÍTULO / TITLE: - Modulating Roles of Amiloride in Irradiation-Induced Antiproliferative Effects in Glioblastoma Multiforme Cells Involving Akt Phosphorylation and the Alternative Splicing of Apoptotic Genes.

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

REVISTA / JOURNAL: - DNA Cell Biol. 2013 Jul 3.

●● [Enlace al texto completo \(gratis o de pago\) 1089/dna.2013.1998](#)

AUTORES / AUTHORS: - Tang JY; Chang HW; Chang JG

INSTITUCIÓN / INSTITUTION: - 1 Department of Radiation Oncology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University , Kaohsiung, Taiwan .

RESUMEN / SUMMARY: - Apoptosis is a key mechanism for enhanced cellular radiosensitivity in radiation therapy. Studies suggest that Akt signaling may play a role in apoptosis and radioresistance. This study evaluates the possible modulating role of amiloride, an antihypertensive agent with a modulating effect to alternative splicing for regulating apoptosis, in the antiproliferative effects induced by ionizing radiation (IR) in glioblastoma multiforme (GBM) 8401 cells. Analysis of cell viability showed that amiloride treatment significantly inhibited cell proliferation in irradiated GBM8401 cells ($p < 0.05$) in a time-dependent manner, especially in cells treated with amiloride with IR post-treatment. In comparison with GBM8401 cells treated with amiloride alone, with GBM8401 cells treated with IR alone, and with human embryonic lung fibroblast control cells (HEL 299), GBM8401 cells treated with IR combined with amiloride showed increased overexpression of phosphorylated Akt, regardless of whether IR treatment was performed before or after amiloride administration. The alternative splicing pattern of apoptotic protease-activating factor-1 (APAF1) in cells treated with amiloride alone, IR alone, and combined amiloride-IR treatments showed more consistent cell proliferation compared to that in other apoptosis-related genes such as baculoviral IAP repeat containing 5 (BIRC5), Bcl-X, and homeodomain interacting protein kinase-3 (HIPK3). In GBM8401 cells treated with amiloride with IR post-treatment, the ratio of pro-survival (-XL,-LC) to pro-apoptotic (-LN,-S) splice variants of APAF1 was lower than that seen in cells treated with amiloride with IR pretreatment, suggesting that pro-apoptotic splice variants of APAF1 (APAF1-LN,-S) were higher in the glioblastoma cells treated with amiloride with IR post-treatment, as compared to glioblastoma cells and fibroblast control cells that had received other treatments. Together, these results suggest that amiloride modulates cell radiosensitivity involving the Akt phosphorylation and the alternative splicing of APAF1, especially for the cells treated with amiloride with IR post-treatment. Therefore, amiloride may improve the effectiveness of radiation therapy for GBMs.

[280]

TÍTULO / TITLE: - The anticancer potential of flavonoids isolated from the stem bark of *Erythrina suberosa* through induction of apoptosis and inhibition of STAT signaling pathway in human leukemia HL-60 cells.

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

REVISTA / JOURNAL: - Chem Biol Interact. 2013 Jul 9;205(2):128-137. doi: 10.1016/j.cbi.2013.06.020.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.06.020](#)

AUTORES / AUTHORS: - Kumar S; Pathania AS; Saxena AK; Vishwakarma RA; Ali A; Bhushan S

INSTITUCIÓN / INSTITUTION: - Division of Natural Product Chemistry, Indian Institute of Integrative Medicine, CSIR, Canal Road, Jammu 180001, India.

RESUMEN / SUMMARY: - *Erythrina suberosa* is an ornamental tall tree found in India, Pakistan, Nepal, Bhutan, Burma, Thailand and Vietnam. We have isolated four known distinct metabolites designated as alpha-Hydroxyerysotrine, 4'-Methoxy licoflavone (MLF), Alpinumisoflavone (AIF) and Wighteone. Among the four isolated metabolites the two flavonoids, MLF and AIF were found to be the most potent cytotoxic agent with IC₅₀ of approximately 20 μM in human leukemia HL-60 cells. We are reporting first time the anticancer and apoptotic potential of MLF and AIF in HL-60 cells. Both MLF and AIF inhibited HL-60 cell proliferation and induce apoptosis as measured by several biological endpoints. MLF and AIF induce apoptosis bodies formation, enhanced annexinV-FITC binding of the cells, increased sub-G₀ cell fraction, loss of mitochondrial membrane potential (Δψ_m), release of cytochrome c, Bax, activation of caspase-9, caspase-3 and PARP (poly ADP Ribose polymers) cleavage in HL-60 cells. MLF and AIF also increase the expression of apical death receptor, Fas, with inhibition of anti-apoptotic protein Bid. All the above parameters revealed that these two flavonoids induce apoptosis through both extrinsic and intrinsic apoptotic pathways in HL-60 cells. In spite of apoptosis, these two flavonoids significantly inhibit nuclear transcription factor NF-κB and STAT (Signal Transducer and Activator of Transcription) signaling pathway, which are highly expressed in leukemia. The present study provide an insight of molecular mechanism of cell death induced by MLF and AIF in HL-60 cells which may be useful in managing and treating leukemia.

[281]

TÍTULO / TITLE: - Inhibition of polyamine oxidase prevented cyclin-dependent kinase inhibitor-induced apoptosis in HCT 116 colon carcinoma cells.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0885-](#)

[8](#)

AUTORES / AUTHORS: - Gurkan AC; Arisan ED; Obakan P; Palavan-Unsal N

INSTITUCIÓN / INSTITUTION: - Molecular Biology and Genetics Department, Science and Literature Faculty, Istanbul Kultur University, Atakoy Campus, 34156, Istanbul, Turkey.

RESUMEN / SUMMARY: - Roscovitine and purvalanol are novel cyclin-dependent kinase (CDK) inhibitors that prevent cell proliferation and induce apoptotic cell death in various cancer cell lines. Although a number of studies have demonstrated the potential apoptotic role of roscovitine, there is limited data about the therapeutic efficiency of purvalanol on cancer cells. The natural polyamines (PAs) putrescine, spermidine, and spermine have essential roles in the regulation of cell differentiation, growth, and proliferation, and increased levels of these compounds have been associated with cancer progression. Recently, depletion of intracellular PA levels because of modulation of PA catabolic enzymes was shown to be an indicator of the efficacy of chemotherapeutic agents. In this study, our aim was to investigate the potential role of PA catabolic enzymes in CDK inhibitor-induced apoptosis in HCT 116 colon carcinoma cells. Exposure of cells to roscovitine or purvalanol decreased cell viability in a dose- and time-dependent manner. The selected concentrations of roscovitine and purvalanol inhibited cell viability by 50 % compared with control cells and induced apoptosis by activating the mitochondria-mediated pathway in a caspase-dependent manner. However, the apoptotic effect of purvalanol was stronger than that of roscovitine in HCT 116 cells. In addition, we found that CDK inhibitors decreased PA levels and significantly upregulated expression of key PA catabolic enzymes such as polyamine oxidase (PAO) and spermine oxidase (SMO). MDL-72,527, a specific inhibitor of PAO and SMO, decreased apoptotic potential of CDK inhibitors on HCT 116 cells. Moreover, transient silencing of PAO was also reduced prevented CDK inhibitor-induced apoptosis in HCT 116 cells. We conclude that the PA catabolic pathway, especially PAO, is a critical target for understanding the molecular mechanism of CDK inhibitor-induced apoptosis.

[282]

TÍTULO / TITLE: - Clinicopathologic Features of Synchronous Colorectal Carcinoma: A Distinct Subset Arising From Multiple Sessile Serrated Adenomas and Associated With High Levels of Microsatellite Instability and Favorable Prognosis.

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

REVISTA / JOURNAL: - Am J Surg Pathol. 2013 Jul 24.

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

[1097/PAS.0b013e31829623b8](#)

AUTORES / AUTHORS: - Hu H; Chang DT; Nikiforova MN; Kuan SF; Pai RK

INSTITUCIÓN / INSTITUTION: - *Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA daggerDepartment of Radiation Oncology, Stanford University, Stanford, CA.

RESUMEN / SUMMARY: - Analysis of synchronous colorectal carcinomas can provide a unique model to examine the underlying molecular alterations in colorectal carcinoma, as synchronous tumors arise in a background of common genetic and environmental factors. We analyzed the clinicopathologic and molecular features of synchronous colorectal carcinomas compared with solitary carcinomas to correlate the histologic findings with molecular alterations and to identify the prognostic significance, if any, of synchronous colorectal carcinoma. Of the 4760 primary colorectal carcinomas resected for the years 2002 to 2012 at our institution, 58 patients (1.2%) harbored 2 invasive primary adenocarcinomas and comprise the synchronous colorectal carcinoma study group. A control group of consecutively resected solitary colorectal carcinomas from 109 patients was also analyzed. Compared with solitary colorectal carcinomas, synchronous colorectal carcinomas more frequently were identified in older patients (median age 70 vs. 60 y; $P=0.001$), involved the right colon (42/58, 72% vs. 47/109, 43%; $P=0.0003$), were more often microsatellite instability-high (MSI-H) (21/58, 36% vs. 13/109, 12%; $P=0.0005$), and were more frequently associated with precursor sessile serrated adenomas (SSAs) (13/58, 22% vs. 2/109, 2%; $P=0.0001$). A statistically significant difference in overall survival was identified between patients with synchronous and solitary colorectal carcinomas (5 y overall survival 92% vs. 56%, $P=0.02$). A unique subgroup of 13 synchronous colorectal carcinomas demonstrated tumors arising from SSAs (SSA-associated). All SSA-associated synchronous colorectal carcinomas were seen in patients above 65 years of age, and 12/13 (92%) occurred in women. Most patients (12/13, 92%) with SSA-associated synchronous colorectal carcinomas demonstrated involvement of the right colon, and tumors were frequently stage I or II (9/13, 69%) and low grade (11/13, 85%). In 12/13 (92%) SSA-associated synchronous colorectal carcinomas, both tumors exhibited loss of MLH1 and PMS2 immunohistochemical expression with concurrent BRAF V600E mutation. Nine of 13 (69%) patients with SSA-associated colorectal carcinoma harbored additional SSAs. Three of 13 (15%) patients with SSA-associated synchronous colorectal carcinoma met the World Health Organization criteria for serrated polyposis. Notably, no patient with SSA-associated synchronous colorectal carcinoma developed disease recurrence or died of disease at last follow-up. In conclusion, synchronous colorectal carcinomas are enriched with MSI-H tumors, particularly those arising from SSAs, which contributes to the overall improved survival for patients with synchronous tumors compared with patients with solitary tumors. We demonstrate that SSA-associated synchronous colorectal carcinomas have a striking predilection for elderly women, are associated with a favorable prognosis, and are MSI-H and BRAF V600E positive.

[283]

TÍTULO / TITLE: - Detectable Wilms' Tumor-1 Transcription at Treatment Completion Is Associated with Poor Prognosis of Acute Myeloid Leukemia: A Single Institution's Experience.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3335-40.

AUTORES / AUTHORS: - Yamauchi T; Negoro E; Lee S; Takai M; Matsuda Y; Takagi K; Kishi S; Tai K; Hosono N; Tasaki T; Ikegaya S; 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: - Background/Aim: The present retrospective study was conducted to measure Wilms' tumor-1 (WT1) mRNA levels in the peripheral blood of patients with acute myeloid leukemia (AML) in order to examine any association with the clinical outcomes. PATIENTS AND METHODS: A total of 58 AML patients were evaluated retrospectively in our institution. WT1 transcripts were determined by real-time reverse transcriptase-polymerase chain reaction in peripheral blood samples. RESULTS: WT1 levels at diagnosis did not vary according to response of induction treatments, and the levels were comparable between the patients with durable remission and the patients with relapse of disease. WT1 levels at the completion of the treatment were higher in the group with relapse of disease than in the group with sustained remission. Detectable WT1 transcripts after the completion of chemotherapy courses were associated with poor prognoses. CONCLUSION: WT1 mRNA levels at treatment completion may predict for prognosis of AML.

[284]

TÍTULO / TITLE: - Dephosphorylation of d-Peptide Derivatives to Form Biofunctional, Supramolecular Nanofibers/Hydrogels and Their Potential Applications for Intracellular Imaging and Intratumoral Chemotherapy.

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

REVISTA / JOURNAL: - J Am Chem Soc. 2013 Jul 3;135(26):9907-14. doi: 10.1021/ja404215g. Epub 2013 Jun 21.

●● Enlace al texto completo (gratis o de pago) [1021/ja404215g](#)

AUTORES / AUTHORS: - Li J; Gao Y; Kuang Y; Shi J; Du X; Zhou J; Wang H; Yang Z; Xu B

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, Brandeis University, 415 South Street, Waltham, Massachusetts 02454, United States.

RESUMEN / SUMMARY: - d-Peptides, as the enantiomers of the naturally occurring l-peptides, usually resist endogenous proteases and are presumably

insensitive to most enzymes. But, it is unclear whether or how a phosphatase catalyzes the dephosphorylation from d-peptides. In this work, we examine the formation of the nanofibers of d-peptides via enzymatic dephosphorylation. By comparing the enzymatic hydrogelation of l-peptide and d-peptide based hydrogelators, we find that the chirality of the precursors of the hydrogelators affects little on the enzymatic hydrogelation resulted from the removal of the phosphate group from a tyrosine phosphate residue. The attachment of a therapeutic agent (e.g., taxol) or a fluorophore (e.g., 4-nitro-2,1,3-benzoxadiazole) to the d-peptide based hydrogelators affords a new type of biostable or biocompatible hydrogelators, which may find applications in intratumoral chemotherapy or intracellular imaging, respectively. This work, as the first comprehensive and systematic study of the unexpected enzymatic dephosphorylation of d-peptides, illustrates a useful approach to generate supramolecular hydrogels that have both biostability and other desired functions.

[285]

TÍTULO / TITLE: - Epigenetic silencing of DACH1 induces loss of transforming growth factor-beta1 antiproliferative response in human hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Hepatology. 2013 Jun 20. doi: 10.1002/hep.26587.

●● Enlace al texto completo (gratis o de pago) [1002/hep.26587](#)

AUTORES / AUTHORS: - Zhu H; Wu K; Yan W; Hu L; Yuan J; Dong Y; Li Y; Jing K; Yang Y; Guo M

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology and Hepatology, Chinese PLA General Hospital, #28 Fuxing Road, Beijing 100853, China.

RESUMEN / SUMMARY: - Human Dachshund homologue 1 (DACH1) is a major component of the Retinal Determination Gene Network (RDGN) and functions as a tumor suppressor. However, the regulation of DACH1 expression and its function in hepatocellular carcinoma (HCC) remain unclear. In this study, epigenetic changes of DACH1 were analyzed in HCC cell lines and primary cancers. We found that promoter region hypermethylation was correlated with loss or reduction of DACH1 expression, and restoration of DACH1 expression was induced by 5-aza-2'-deoxycytidine (5-AZA) in HCC cell lines. Promoter region methylation was found in 42% of primary HCC. Reduced expression of DACH1 was associated with poor differentiation of HCC nodules and higher serum aspartate aminotransferase/alanine aminotransferase ratio. DACH1 suppressed cellular growth by reactivating TGF-beta signaling. Ectopic expression of DACH1 enhanced chemosensitivity to 5-fluorouracil (5-FU) by inducing p21 expression in HCC cells. Conclusion: DACH1 is frequently methylated in HCC and DACH1 expression is regulated by promoter hypermethylation. Down regulation of DACH1 is a novel mechanism for gaining

resistance to the anti-proliferative signaling of TGF-beta1 and 5-FU resistance. (HEPATOLOGY 2013.).

[286]

TÍTULO / TITLE: - Silencing of the Smad nuclear interacting protein 1 (SNIP1) by siRNA inhibits proliferation and induces apoptosis in pituitary adenoma cells.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0873-](#)

[1](#)

AUTORES / AUTHORS: - Chen X; Xue F; Xie T; Luo C

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Changzheng Hospital, Second Military Medical University, No. 415 FengYang Road, Shanghai, 200003, China.

RESUMEN / SUMMARY: - Smad nuclear interacting protein 1 (SNIP1) gene encodes a protein that contains a conservative C-terminal forkhead-associated domain and functions as a transcriptional coactivator to regulate cell proliferation and cancer progression. This study aimed to investigate the clinical and biological significance of SNIP1 expression in pituitary adenoma. We analyzed SNIP1 expressions in mouse fibroblast L929 cells and mouse pituitary adenoma AtT-20 cells by Western blotting. SNIP1 gene knockdown by small interfering RNA (siRNA) transfection was performed to evaluate SNIP1 function in pituitary adenoma cell lines. As expected, SNIP1 was found to be upregulated in pituitary adenoma cells. The mRNA and protein levels of SNIP1 were inhibited in AtT-20 cells transfected with siRNAs, which led to decreased proliferation, increased apoptosis, and cycle arrest of pituitary adenoma cells. Concomitantly, c-Myc and cyclin D1 protein levels were reduced. These findings may provide novel targets for the treatment of pituitary adenoma.

[287]

TÍTULO / TITLE: - Essential role for the Mnk-pathway in the inhibitory effects of Type I interferons on myeloproliferative neoplasm (MPN) precursors.

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

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

●● Enlace al texto completo (gratis o de pago) [1074/jbc.M113.476192](#)

AUTORES / AUTHORS: - Mehrotra S; Sharma B; Joshi S; Kroczyńska B; Majchrzak B; Stein BL; McMahon B; Altman JK; Licht JD; Baker DP; Eklund EA; Wickrema A; Verma A; Fish EN; Platanias LC

INSTITUCIÓN / INSTITUTION: - Northwestern University, United States;

RESUMEN / SUMMARY: - The mechanisms of generation of the antineoplastic effects of interferons (IFNs) in malignant hematopoietic cells remain to be precisely defined. We examined the activation of Type I IFN-dependent

signaling pathways in malignant cells transformed by Jak2V617F, a critical pathogenic mutation in myeloproliferative neoplasms (MPNs). Our studies demonstrate that during engagement of the Type I IFN receptor (IFNAR) there is activation of Jak-Stat pathways and also engagement of Mnk kinases. Activation of Mnk kinases is regulated by the Mek/Erk pathway and is required for the generation of IFN-induced growth inhibitory responses, but Mnk kinase activation does not modulate IFN-regulated Jak-Stat signals. We demonstrate that in order for Type I IFNs to exert suppressive effects in malignant hematopoietic progenitors from patients with Polycythemia Vera (PV), induction of Mnk kinase activity is required, as evidenced by studies involving pharmacological inhibition of Mnk or siRNA-mediated Mnk knock-down. Altogether, these findings provide evidence for key and essential roles of the Mnk kinase pathway in the generation of the antineoplastic effects of Type I IFNs in Jak2V617F- dependent MPNs.

[288]

TÍTULO / TITLE: - Curcumin induces apoptosis in human gastric carcinoma AGS cells and colon carcinoma HT-29 cells through mitochondrial dysfunction and endoplasmic reticulum stress.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0871-](http://1007/s10495-013-0871-1)

[1](#)

AUTORES / AUTHORS: - Cao A; Li Q; Yin P; Dong Y; Shi H; Wang L; Ji G; Xie J; Wu D

INSTITUCIÓN / INSTITUTION: - Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China.

RESUMEN / SUMMARY: - In the present study, we investigate the effect of curcumin, a major active component isolated from rhizomes of *Curcuma longa*, on the cytotoxicity of three human carcinoma cell lines (AGS, HT-29 and MGC803) in gastrointestinal tract and a normal gastric epithelial cell line GES-1, and the mechanism of curcumin-induced apoptosis. The results indicated that curcumin inhibited the gastrointestinal carcinoma cell growth in a dose-dependent manner and cytotoxicity was more towards the gastric carcinoma cell AGS and colon carcinoma cell HT-29 compared to normal gastric cell GES-1, and increased externalization of phosphatidylserine residue was observed by Annexin V/PI staining in the two cell lines. Treatment of AGS and HT-29 cells with curcumin enhanced the cleavage of procaspase-3, -7, -8 and -9. Meanwhile, curcumin induced endoplasmic reticulum (ER) stress and mitochondrial dysfunction as evidenced by up-regulation of CCAAT/enhancer binding protein homologous protein (CHOP), phosphorylation of JNK and down-regulation of SERCA2ATPase, release of cytochrome c, decrease of Bcl-2 and reduction of mitochondrial membrane potential in both AGS and HT-29

cells. Overexpression of bax, total JNK, phospho-FADD and total FADD were also observed in curcumin-treated HT-29 cells. Moreover, curcumin decreased cytosolic and ER Ca²⁺, but increased mitochondrial Ca²⁺ in the two cell lines. 2-Aminoethoxydiphenyl borate, an antagonist of inositol 1, 4, 5-triphosphate receptor, partly blocked curcumin-induced cytosolic Ca²⁺ decrease in AGS and HT-29 cells. Additionally, carbonyl cyanide m-chlorophenylhydrazone, an inhibitor of mitochondrial Ca²⁺ uptake, reversed curcumin-triggered AGS and HT-29 cells growth inhibition. siRNA to CHOP markedly reduced curcumin-induced apoptosis. These results suggest that curcumin can impact on ER stress and mitochondria functional pathways in AGS and HT-29 cells, death receptor pathway was also involved in curcumin-treated HT-29 cells, thus identifying specific well-defined molecular mechanisms that may be targeted by therapeutic strategies.

[289]

TÍTULO / TITLE: - A 26-Gene Hypoxia Signature Predicts Benefit from Hypoxia-Modifying Therapy in Laryngeal Cancer but Not Bladder Cancer.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 6.

- Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-13-0542](#)

AUTORES / AUTHORS: - Eustace A; Mani N; Span PN; Irlam JJ; Taylor J; Betts GN; Denley H; Miller CJ; Homer JJ; Rojas AM; Hoskin PJ; Buffa FM; Harris AL; Kaanders JH; West CM

INSTITUCIÓN / INSTITUTION: - Author Affiliations: Translational Radiobiology Group, Institute of Cancer Sciences, University of Manchester, Christie Hospital, Departments of Otolaryngology-Head and Neck Surgery and Pathology, Manchester Royal Infirmary, Manchester Academic Health Sciences Centre; Applied Computational Biology & Bioinformatics Group, Paterson Institute for Cancer Research, Manchester; Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex; and Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; and Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

RESUMEN / SUMMARY: - PURPOSE: Tumor hypoxia is associated with a poor prognosis, hypoxia modification improves outcome, and hypoxic status predicts benefit from treatment. Yet, there is no universal measure of clinical hypoxia. The aim of this study was to investigate whether a 26-gene hypoxia signature predicted benefit from hypoxia-modifying treatment in both cancer types. EXPERIMENTAL DESIGN: Samples were available from 157 T2-T4 laryngeal cancer and 185 T1-T4a bladder cancer patients enrolled on the accelerated radiotherapy with carbogen and nicotinamide (ARCON) and bladder carbogen nicotinamide (BCON) phase III randomized trials of

radiotherapy alone or with carbogen and nicotinamide (CON) respectively. Customized TaqMan low density arrays (TLDA) were used to assess expression of the 26-gene signature using quantitative real-time PCR. The median expression of the 26 genes was used to derive a hypoxia score (HS). Patients were categorized as TLDA-HS low (\leq median) or TLDA-HS high ($>$ median). The primary outcome measures were regional control (RC; ARCON) and overall survival (BCON).RESULTS: Laryngeal tumors categorized as TLDA-HS high showed greater benefit from ARCON than TLDA-HS low tumors. Five-year RC was 81% (radiotherapy alone) versus 100% (CON) for TLDA-HS high ($P = 0.009$). For TLDA-HS low, 5-year RC was 91% (radiotherapy alone) versus 90% (CON; $P = 0.90$). TLDA-HS did not predict benefit from CON in bladder cancer.CONCLUSION: The 26-gene hypoxia signature predicts benefit from hypoxia-modifying treatment in laryngeal cancer. These findings will be evaluated in a prospective clinical trial. Clin Cancer Res; 1-10. ©2013 AACR.

[290]

TÍTULO / TITLE: - Lamin B1 Is a Novel Therapeutic Target of Betulinic Acid in Pancreatic Cancer.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 15.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3630](#)

AUTORES / AUTHORS: - Li L; Du Y; Kong X; Li Z; Jia Z; Cui J; Gao J; Wang L; Xie K

INSTITUCIÓN / INSTITUTION: - GI Medical Oncology, MD Anderson Cancer Center.

RESUMEN / SUMMARY: - PURPOSE: Betulinic acid (BA), a naturally occurring pentacyclic triterpenoid, exhibits potent anti-tumor activities, whereas the underlying mechanisms remain unclear. In current study, we sought to determine the role and regulation of lamin B1 expression in human pancreatic cancer pathogenesis and BA-based therapy. EXPERIMENTAL DESIGN: We used cDNA microarray to identify BA target genes and used tissue microarray to determine the expression levels of lamin B1 in pancreatic cancer tissues and to define their relationship with the clinicopathologic characteristics of pancreatic cancer. We also used in vitro and in vivo models to determine the biological impacts of altered lamin B1 expression on and mechanisms underlying lamin B1 overexpression in human pancreatic cancer. RESULTS: We found that lamin B1 was significantly downregulated by BA treatment in pancreatic cancer in both in vitro culture and xenograft models. Overexpression of lamin B1 was pronounced in human pancreatic cancer and increased lamin B1 expression was directly associated with low grade differentiation, increased incidence of distant metastasis and poor prognosis of pancreatic cancer patients. Furthermore, knockdown of lamin B1 significantly attenuated the

proliferation, invasion and tumorigenicity of pancreatic cancer cells.
CONCLUSIONS: Lamin B1 plays an important role in pancreatic cancer pathogenesis and is a novel therapeutic target of BA treatment.

[291]

TÍTULO / TITLE: - Hugl-1 induces apoptosis in esophageal carcinoma cells both in vitro and in vivo.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Jul 14;19(26):4127-36. doi: 10.3748/wjg.v19.i26.4127.

●● Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i26.4127](#)

AUTORES / AUTHORS: - Song J; Peng XL; Ji MY; Ai MH; Zhang JX; Dong WG

INSTITUCIÓN / INSTITUTION: - Jia Song, Xiu-Lan Peng, Meng-Yao Ji, Ming-Hua Ai, Ji-Xiang Zhang, Wei-Guo Dong, Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei Province, China.

RESUMEN / SUMMARY: - AIM: To determine whether the human giant larvae homolog 1 gene (Hugl-1/Llg1/Lgl1) exerts tumor suppressor effects in esophageal cancer. METHODS: We constructed a Hugl-1 expression plasmid, pEZ-M29-Hugl1, for gene transfection. We transfected the pEZ-M29-Hugl1 plasmid into Eca109 esophageal cancer cell lines with Lipofectamine 2000 to overexpress Hugl-1. Real-time reverse transcription-polymerase chain reaction (RT-PCR) and Western blotting were performed to determine the effects of the plasmid on Hugl-1 expression. In vitro cell proliferation and apoptosis were examined separately by cell counting Kit-8 (CCK-8) assay, flow cytometry, and Western blotting before and after the transfection of the plasmid into Eca109 cells. Cell cycle distribution was assessed with flow cytometry. The effect of Hugl-1 overexpressing on tumor growth in vivo was performed with a xenograft tumor model in nude mice. Expression of Hugl-1 in xenograft tumor was analyzed by immunohistochemistry. The transferase-mediated dUTP nick end-labeling (TUNEL) technique was performed to detect and quantitate apoptotic cell. RESULTS: The transfection efficiency was confirmed with real-time RT-PCR and Western blotting. Our results show that compared with control groups the mRNA levels and protein levels of Hugl-1 in pEZ-M29-Hugl1-treated group were remarkably increased ($P < 0.05$). The CCK-8 assay demonstrated that the growth of cells overexpressing Hugl-1 was significantly lower than control cells. Cell cycle distribution showed there was a G0/G1 cell cycle arrest in cells overexpressing Hugl-1 (64.09% +/- 3.14% vs 50.32% +/- 4.60%, 64.09% +/- 3.14% vs 49.13% +/- 2.24%). Annexin V-fluorescein isothiocyanate revealed that apoptosis was significantly increased in cells overexpressing Hugl-1 compared with control group (17.33% +/- 4.76% vs 6.90% +/- 1.61%, 17.33% +/- 4.76% vs 6.27% +/- 0.38%). Moreover, we found that Hugl-1 changes the level of the anti-apoptotic protein Bcl-2 and the pro-apoptotic protein Bax and the activation of both caspase-3 and caspase-9. With a TUNEL assay, we found

that Hugi-1 markedly increased the apoptosis rate of Eca109 cells in vivo (60.50% +/- 9.11% vs 25.00% +/- 12.25%). It was shown that Hugi-1 represents a significantly more effective tumor suppressor gene alone in a xenograft tumor mouse model. This data suggest that Hugi-1 inhibited tumor growth and induced cell apoptosis in vivo. CONCLUSION: These results suggest that Hugi-1 induces growth suppression and apoptosis in a human esophageal squamous cell carcinoma cell line both in vitro and in vivo.

[292]

TÍTULO / TITLE: - FTY720 induces apoptosis of chronic myelogenous leukemia cells via dual activation of BIM and BID and overcomes various types of resistance to tyrosine kinase inhibitors.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jul 14.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0882-](#)

[y](#)

AUTORES / AUTHORS: - Kiyota M; Kuroda J; Yamamoto-Sugitani M; Shimura Y; Nakayama R; Nagoshi H; Mizutani S; Chinen Y; Sasaki N; Sakamoto N; Kobayashi T; Matsumoto Y; Horiike S; Taniwaki M

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyoku, Kyoto, 602-8566, Japan.

RESUMEN / SUMMARY: - PP2A activator FTY720 has been shown to possess the anti-leukemic activity for chronic myelogenous leukemia (CML), however, the cell killing mechanism underlying its anti-leukemic activity has remained to be verified. We investigated the precise mechanisms underlying the apoptosis induction by FTY720, especially focusing on the roles of BH3-only proteins, and the therapeutic potency of FTY720 for CML. Enforced expression of either BCL2 or the dominant-negative protein of FADD (FADD.DN) partly protected CML cells from apoptosis by FTY720, indicating the involvement of both cell extrinsic and intrinsic apoptosis pathways. FTY720 activates pro-apoptotic BH3-only proteins: BIM, which is essential for apoptosis by BCR-ABL1 tyrosine kinase inhibitors (TKIs), and BID, which accelerates the extrinsic apoptosis pathway. Gene knockdown of either BIM or BID partly protected K562 cells from apoptosis by FTY720, but the extent of cell protection was not as much as that by overexpression of either BCL2 or FADD.DN. Moreover, knockdown of both BIM and BID did not provide additional protection compared with knockdown of only BIM or BID, indicating that BIM and BID complement each other in apoptosis by FTY720, especially when either is functionally impaired. FTY720 can overcome TKI resistance caused by ABL kinase domain mutations, dysfunction of BIM resulting from gene deletion polymorphism, and galectin-3 overexpression. In addition, ABT-263, a BH3-mimetic, significantly augmented cell death induction by FTY720 both in TKI-sensitive and -resistant leukemic

cells. These results provide the rationale that FTY720, with its unique effects on BIM and BID, could lead to new therapeutic strategies for CML.

[293]

TÍTULO / TITLE: - Pattern of breast cancer susceptibility gene 1 expression is a potential prognostic biomarker in resectable pancreatic ductal adenocarcinoma.

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

REVISTA / JOURNAL: - Pancreas. 2013 Aug;42(6):977-82. doi: 10.1097/MPA.0b013e318287885c.

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

[1097/MPA.0b013e318287885c](#)

AUTORES / AUTHORS: - Wang T; Wentz SC; Ausborn NL; Washington MK; Merchant N; Zhao Z; Shyr Y; Chakravarthy AB; Xia F

INSTITUCIÓN / INSTITUTION: - From the *Department of Radiation Oncology, daggerDepartment of Pathology, double daggerDepartment of Surgery, and section signDepartment of Biostatistics, School of Medicine, Vanderbilt University, Nashville, TN; and parallelDepartment of Radiation Oncology, College of Medicine, The Ohio State University, Columbus, OH.

RESUMEN / SUMMARY: - **OBJECTIVES:** The tumor-suppressor breast cancer susceptibility gene 1 (BRCA1) is a nuclear-cytoplasmic shuttling protein that when in the nucleus is required for DNA repair whereas when in the cytoplasm is important in activating cell death processes. Although BRCA1 mutations have been shown to be associated with an increased risk of pancreatic ductal adenocarcinoma (PDAC), its role in disease progression is yet to be determined. We hypothesized that BRCA1 expression pattern could be used as a prognostic biomarker. **METHODS:** Sixty-seven patients who underwent resections for PDAC were included. A tissue microarray was constructed, stained with antibodies to BRCA1, and scored for intensity and subcellular location. Univariate and multivariate statistical analyses were performed. **RESULTS:** An increase in cytosolic BRCA1 distribution was associated with higher pathologic stage ($P = 0.006$). Nuclear-cytoplasmic BRCA1 distribution was associated with a decrease in recurrence-free survival with a hazards ratio of 1.4 ($P = 0.059$). Decreased BRCA1 intensity was associated with higher pathologic stage ($P = 0.027$), but BRCA1 intensity was not associated with overall survival or recurrence-free survival. **CONCLUSIONS:** Our results demonstrate a possible association of BRCA1 expression pattern with pathologic stage, implying a potential role of BRCA1 in PDAC development and progression.

[294]

TÍTULO / TITLE: - CAPE promotes TRAIL-induced apoptosis through the upregulation of TRAIL receptors via activation of p38 and suppression of JNK in SK-Hep1 hepatocellular carcinoma cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Jul 15. doi: 10.3892/ijo.2013.2018.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2018](#)

AUTORES / AUTHORS: - Kim EY; Ryu JH; Kim AK

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Republic of Korea.

RESUMEN / SUMMARY: - Caffeic acid phenethyl ester (CAPE), a phenolic compound derived from honeybee propolis, has been reported to possess anticancer activities in several types of malignant cells. Here, we show that treatment with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in combination with CAPE significantly sensitized SK-Hep1 cells to TRAIL-induced apoptosis. The sensitization to TRAIL was accompanied by the activation of extrinsic and intrinsic apoptotic pathways, leading to the activation of caspases, mitochondrial disruption and PARP cleavage. Moreover, TRAIL receptors, such as DR4 and DR5 were significantly upregulated by CAPE treatment, and both DR4/Fc and DR5/Fc chimera markedly abrogated apoptosis induced by CAPE and TRAIL, demonstrating the critical role of these death receptors in combination-induced apoptosis. The effect of CAPE on mitogen-activated protein kinases (MAPKs) was further examined, where CAPE treatment resulted in the activation of p38 and the inhibition of JNK, without affecting levels of phospho-ERK. Our results showed that p38 and JNK exhibited the opposite role in SK-Hep1 cells. The inhibition of p38, using SB203580, blocked the CAPE-induced expression of death receptors and attenuated the combination-induced apoptosis, suggesting the pro-apoptotic role of p38. In contrast, JNK-specific inhibition, by SP600125, triggered upregulation of DR4 and DR5, and sensitized SK-Hep1 cells to TRAIL, indicating that the CAPE-induced suppression of JNK may contribute to the sensitizing effect of CAPE through the upregulation of death receptors. Taken together, these results indicate that CAPE potentiated TRAIL-induced apoptosis in SK-Hep1 cells, through upregulation of TRAIL receptors via modulation of p38 and JNK signaling pathways.

[295]

TÍTULO / TITLE: - Discovery of colorectal cancer PIK3CA mutation as potential predictive biomarker: power and promise of molecular pathological epidemiology.

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

REVISTA / JOURNAL: - Oncogene. 2013 Jun 24. doi: 10.1038/onc.2013.244.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.244](#)

AUTORES / AUTHORS: - Ogino S; Lochhead P; Giovannucci E; Meyerhardt JA; Fuchs CS; Chan AT

INSTITUCIÓN / INSTITUTION: - 1] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA [2] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA [3] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

RESUMEN / SUMMARY: - Regular use of aspirin reduces incidence and mortality of various cancers, including colorectal cancer. Anticancer effect of aspirin represents one of the 'Provocative Questions' in cancer research. Experimental and clinical studies support a carcinogenic role for PTGS2 (cyclooxygenase-2), which is an important enzymatic mediator of inflammation, and a target of aspirin. Recent 'molecular pathological epidemiology' (MPE) research has shown that aspirin use is associated with better prognosis and clinical outcome in PIK3CA-mutated colorectal carcinoma, suggesting somatic PIK3CA mutation as a molecular biomarker that predicts response to aspirin therapy. The PI3K (phosphatidylinositol-4,5-bisphosphonate 3-kinase) enzyme has a pivotal role in the PI3K-AKT signaling pathway. Activating PIK3CA oncogene mutations are observed in various malignancies including breast cancer, ovarian cancer, brain tumor, hepatocellular carcinoma, lung cancer and colon cancer. The prevalence of PIK3CA mutations increases continuously from rectal to cecal cancers, supporting the 'colorectal continuum' paradigm, and an important interplay of gut microbiota and host immune/inflammatory reaction. MPE represents an interdisciplinary integrative science, conceptually defined as 'epidemiology of molecular heterogeneity of disease'. As exposome and interactome vary from person to person and influence disease process, each disease process is unique (the unique disease principle). Therefore, MPE concept and paradigm can extend to non-neoplastic diseases including diabetes mellitus, cardiovascular diseases, metabolic diseases, and so on. MPE research opportunities are currently limited by paucity of tumor molecular data in the existing large-scale population-based studies. However, genomic, epigenomic and molecular pathology testings (for example, analyses for microsatellite instability, MLH1 promoter CpG island methylation, and KRAS and BRAF mutations in colorectal tumors) are becoming routine clinical practices. In order for integrative molecular and population science to be routine practice, we must first reform education curricula by integrating both population and molecular biological sciences. As consequences, next-generation hybrid molecular biological and population scientists can advance science, moving closer to personalized precision medicine and health care. Oncogene advance online publication, 24 June 2013; doi:10.1038/onc.2013.244.

[296]

TÍTULO / TITLE: - Metastasis-associated protein 1 is a novel marker predicting survival and lymph nodes metastasis in cervical cancer.

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

REVISTA / JOURNAL: - Hum Pathol. 2013 Jul 15. pii: S0046-8177(13)00197-4. doi: 10.1016/j.humpath.2013.05.009.

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

[1016/j.humpath.2013.05.009](#)

AUTORES / AUTHORS: - Liu T; Yang M; Yang S; Ge T; Gu L; Lou G

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, The Third Affiliated Hospital, Harbin Medical University, Harbin 150040, China.

RESUMEN / SUMMARY: - Metastasis-associated gene 1 (MTA1), which is involved in tumor progression, metastasis, and angiogenesis, has been examined in several malignant tumors. However, the expression and the effect of MTA1 on human cervical cancer remain unknown. In this study, we investigated the level of MTA1 expression in cervical carcinoma and its clinical significance. By immunohistochemical staining, the correlation of MTA1 overexpression with clinical features and patient outcome was analyzed in 132 formalin-fixed, paraffin-embedded cervical cancer tissues. MTA1 protein overexpression was detected in 73 (55.3%) of 132 patients. High levels of MTA1 protein were clearly correlated with histologic grade ($P = .006$), lymph node metastasis ($P = .001$), and recurrence ($P = .016$). Multivariate Cox analysis showed that MTA1 was an independent factor for overall survival (hazard ratio, 3.486; 95% confidence interval [CI], 1.274-9.537; $P = .015$) and disease-free survival (hazard ratio, 3.373; 95% CI, 1.212-9.387; $P = .020$). Multivariate logistic regression analysis indicated that elevated MTA1 was strongly associated with lymph node metastasis (odds ratio, 3.879; 95% CI, 1.391-10.816; $P = .010$). Sensitivity and specificity were calculated as 81.25% and 53.0%, respectively. These findings suggest that MTA1 nuclear overexpression is associated with tumor progression and metastasis and thus support its clinical significance in future gene-targeted therapies, particularly the management of patients with cervical cancer.

[297]

TÍTULO / TITLE: - P-glycoprotein-dependent resistance of cancer cells toward the extrinsic TRAIL apoptosis signaling pathway.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Jun 14. pii: S0006-2952(13)00359-6. doi: 10.1016/j.bcp.2013.06.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.06.004](#)

AUTORES / AUTHORS: - Galski H; Oved-Gelber T; Simanovsky M; Lazarovici P; Gottesman MM; Nagler A

INSTITUCIÓN / INSTITUTION: - Laboratory of Molecular Immunology, Division of Hematology, Chaim Sheba Medical Center, Tel Hashomer, Israel. Electronic address: hgalski@sheba.health.gov.il.

RESUMEN / SUMMARY: - The TNF-related apoptosis-inducing ligand (TRAIL or Apo2L) preferentially cause apoptosis of malignant cells in vitro and in vivo without severe toxicity. Therefore, TRAIL or agonist antibodies to the TRAIL DR4 and DR5 receptors are used in cancer therapy. However, many malignant cells are intrinsically resistant or acquire resistance to TRAIL. It has been previously proposed that the multidrug transporter P-glycoprotein (Pgp) might play a role in resistance of cells to intrinsic apoptotic pathways by interfering with components of ceramide metabolism or by modulating the electrochemical gradient across the plasma membrane. In this study we investigated whether Pgp also confers resistance toward extrinsic death ligands of the TNF family. To this end we focused our study on HeLa cells carrying a tetracycline-repressible plasmid system which shuts down Pgp expression in the presence of tetracycline. Our findings demonstrate that expression of Pgp is a significant factor conferring resistance to TRAIL administration, but not to other death ligands such as TNF-alpha and Fas ligand. Moreover, blocking Pgp transport activity sensitizes the malignant cells toward TRAIL. Therefore, Pgp transport function is required to confer resistance to TRAIL. Although the resistance to TRAIL-induced apoptosis is Pgp specific, TRAIL itself is not a direct substrate of Pgp. Pgp expression has no effect on the level of the TRAIL receptors DR4 and DR5. These findings might have clinical implications since the combination of TRAIL therapy with administration of Pgp modulators might sensitize TRAIL resistant tumors.

[298]

TÍTULO / TITLE: - JAK inhibitors suppress t(8;21) fusion protein-induced leukemia.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jul 1. doi: 10.1038/leu.2013.197.

●● [Enlace al texto completo \(gratis o de pago\) 1038/leu.2013.197](#)

AUTORES / AUTHORS: - Lo MC; Peterson LF; Yan M; Cong X; Hickman JH; Dekelver RC; Niewerth D; Zhang DE

INSTITUCIÓN / INSTITUTION: - Moores UCSD Cancer Center, University of California San Diego, La Jolla, CA, USA.

RESUMEN / SUMMARY: - Oncogenic mutations in components of the JAK/STAT pathway, including those in cytokine receptors and JAKs, lead to increased activity of downstream signaling and are frequently found in leukemia and other hematological disorders. Thus, small-molecule inhibitors of this pathway have been the focus of targeted therapy in these hematological diseases. We previously showed that t(8;21) fusion protein acute myeloid leukemia (AML)1-ETO and its alternatively spliced variant AML1-ETO9a (AE9a) enhance the

JAK/STAT pathway via downregulation of CD45, a negative regulator of this pathway. To investigate the therapeutic potential of targeting JAK/STAT in t(8;21) leukemia, we examined the effects of a JAK2-selective inhibitor TG101209 and a JAK1/2-selective inhibitor INCB18424 on t(8;21) leukemia cells. TG101209 and INCB18424 inhibited proliferation and promoted apoptosis of these cells. Furthermore, TG101209 treatment in AE9a leukemia mice reduced tumor burden and significantly prolonged survival. TG101209 also significantly impaired the leukemia-initiating potential of AE9a leukemia cells in secondary recipient mice. These results demonstrate the potential therapeutic efficacy of JAK inhibitors in treating t(8;21) AML. Leukemia advance online publication, 19 July 2013; doi:10.1038/leu.2013.197.

[299]

TÍTULO / TITLE: - Inducing apoptosis of cancer cells using small-molecule plant compounds that bind to GRP78.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 23;109(2):433-43. doi: 10.1038/bjc.2013.325. Epub 2013 Jun 27.

●● [Enlace al texto completo \(gratis o de pago\) 1038/bjc.2013.325](#)

AUTORES / AUTHORS: - Martin S; Lamb HK; Brady C; Lefkove B; Bonner MY; Thompson P; Lovat PE; Arbiser JL; Hawkins AR; Redfern CP

INSTITUCIÓN / INSTITUTION: - Newcastle Cancer Centre at the Northern Institute for Cancer Research, Medical School, Newcastle University, Newcastle upon Tyne NE2 4HH, UK.

RESUMEN / SUMMARY: - Background: Glucose regulated protein 78 (GRP78) functions as a sensor of endoplasmic reticulum (ER) stress. The aim of this study was to test the hypothesis that molecules that bind to GRP78 induce the unfolded protein response (UPR) and enhance cell death in combination with ER stress inducers. Methods: Differential scanning calorimetry (DSC), measurement of cell death by flow cytometry and the induction of ER stress markers using western blotting. Results: Epigallocatechin gallate (EGCG), a flavonoid component of Green Tea *Camellia sinensis*, and honokiol (HNK), a *Magnolia grandiflora* derivative, bind to unfolded conformations of the GRP78 ATPase domain. Epigallocatechin gallate and HNK induced death in six neuroectodermal tumour cell lines tested. Levels of death to HNK were twice that for EGCG; half-maximal effective doses were similar but EGCG sensitivity varied more widely between cell types. Honokiol induced ER stress and UPR as predicted from its ability to interact with GRP78, but EGCG was less effective. With respect to cell death, HNK had synergistic effects on melanoma and glioblastoma cells with the ER stress inducers fenretinide or bortezomib, but only additive (fenretinide) or inhibitory (bortezomib) effects on neuroblastoma cells. Conclusion: Honokiol induces apoptosis due to ER stress from an interaction with GRP78. The data are consistent with DSC results that suggest

that HNK binds to GRP78 more effectively than EGCG. Therefore, HNK may warrant development as an antitumour drug.

[300]

TÍTULO / TITLE: - Knockdown of TIGAR by RNA interference induces apoptosis and autophagy in HepG2 hepatocellular carcinoma cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 26;437(2):300-306. doi: 10.1016/j.bbrc.2013.06.072. Epub 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.06.072](https://doi.org/10.1016/j.bbrc.2013.06.072)

AUTORES / AUTHORS: - Ye L; Zhao X; Lu J; Qian G; Zheng JC; Ge S

INSTITUCIÓN / INSTITUTION: - Laboratory of Neuroimmunology and Regenerative Therapy, Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198-5930, USA; Department of Biochemistry and Molecular Biology, Shanghai Jiaotong University School of Medicine, Shanghai 200025, People's Republic of China; Center for Translational Neurodegeneration and Regenerative Therapy, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200092, People's Republic of China.

RESUMEN / SUMMARY: - Apoptosis and autophagy are crucial mechanisms regulating cell death, and the relationship between apoptosis and autophagy in the liver has yet to be thoroughly explored. TIGAR (TP53-induced glycolysis and apoptosis regulator), which is a p53-inducible gene, functions in the suppression of ROS (reactive oxygen species) and protects U2OS cells from undergoing cell death. In this study, silencing TIGAR by RNAi (RNA interference) in HepG2 cells down-regulated both TIGAR mRNA (approximately 75%) and protein levels (approximately 80%) and led to the inhibition of cell growth ($P < 0.01$) by apoptosis ($P < 0.001$) and autophagy. We demonstrated that TIGAR can increase ROS levels in HepG2 cells. The down-regulation of TIGAR led to the induction of LC-3 II (specific autophagic marker), the formation of the autophagosome, and increased Beclin-1 expression. 3-MA (3-Methyladenine), an inhibitor of autophagic sequestration blocker, inhibited TIGAR siRNA-enhanced autophagy, as indicated by the decrease in LC-3 II levels. Consequently, these data provide the first evidence that targeted silencing of TIGAR induces apoptotic and autophagic cell death in HepG2 cells, and our data raise hope for the future successful application of TIGAR siRNA in patients with hepatocellular carcinoma (HCC).

[301]

TÍTULO / TITLE: - An image-based multi-label human protein subcellular localization predictor (iLocator) reveals protein mislocalizations in cancer tissues.

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

REVISTA / JOURNAL: - Bioinformatics. 2013 Aug 15;29(16):2032-40. doi: 10.1093/bioinformatics/btt320. Epub 2013 Jun 4.

- Enlace al texto completo (gratis o de pago)

[1093/bioinformatics/btt320](#)

AUTORES / AUTHORS: - Xu YY; Yang F; Zhang Y; Shen HB

INSTITUCIÓN / INSTITUTION: - Institute of Image Processing and Pattern Recognition, Shanghai Jiao Tong University, and Key Laboratory of System Control and Information Processing, Ministry of Education of China, Shanghai 200240, China, Department of Computational Medicine and Bioinformatics and Department of Biological Chemistry, University of Michigan, Ann Arbor, MI 48109, USA.

RESUMEN / SUMMARY: - MOTIVATION: Human cells are organized into compartments of different biochemical cellular processes. Having proteins appear at the right time to the correct locations in the cellular compartments is required to conduct their functions in normal cells, whereas mislocalization of proteins can result in pathological diseases, including cancer. RESULTS: To reveal the cancer-related protein mislocalizations, we developed an image-based multi-label subcellular location predictor, iLocator, which covers seven cellular localizations. The iLocator incorporates both global and local image descriptors and generates predictions by using an ensemble multi-label classifier. The algorithm has the ability to treat both single- and multiple-location proteins. We first trained and tested iLocator on 3240 normal human tissue images that have known subcellular location information from the human protein atlas. The iLocator was then used to generate protein localization predictions for 3696 protein images from seven cancer tissues that have no location annotations in the human protein atlas. By comparing the output data from normal and cancer tissues, we detected eight potential cancer biomarker proteins that have significant localization differences with P-value < 0.01. AVAILABILITY: <http://www.csbio.sjtu.edu.cn/bioinf/iLocator/> CONTACT: hbshen@sjtu.edu.cn or zhng@umich.edu SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

[302]

TÍTULO / TITLE: - Risk prediction for malignant conversion of oral epithelial dysplasia by hypoxia related protein expression.

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

REVISTA / JOURNAL: - Pathology. 2013 Aug;45(5):478-83. doi: 10.1097/PAT.0b013e3283632624.

- Enlace al texto completo (gratis o de pago)

[1097/PAT.0b013e3283632624](#)

AUTORES / AUTHORS: - Zhang X; Han S; Han HY; Ryu MH; Kim KY; Choi EJ; Cha IH; Kim J

INSTITUCIÓN / INSTITUTION: - *Oral Cancer Research Institute daggerOral and Maxillofacial Surgery, College of Dentistry, Yonsei University, Seoul double daggerDepartment of Oral Pathology, Brain Korea 21 Project, Yonsei University College of Dentistry, Seoul section signDepartment of Oral Pathology, College of Dentistry, Yangsan Campus of Pusan National University, Pusan, Republic of Korea ||Department of Pathology, Yanbian University Hospital, Yanji City, Jilin Province, China.

RESUMEN / SUMMARY: - AIMS: Increased aerobic glycolysis is a unique finding in cancers and hypoxia-related proteins are associated with aerobic glycolysis. Therefore, we aimed to investigate whether hypoxia-related proteins can be predictive markers for malignant conversion of oral premalignant lesions with epithelial dysplasia (OED). METHODS: Expression of HIF-1alpha, Glut-1 and CA9 were detected in clinical samples of eight normal oral mucosa, 85 transitional areas of oral squamous cell carcinoma (OSCC) and 28 OED with or without malignant conversion using immunohistochemistry and were also comparatively detected in immortalised human oral keratinocyte (IHOK) and OSCC cell lines under hypoxia using immunoblotting. RESULTS: Sequential expression of HIF-1alpha, Glut-1 and CA9 was found both in transitional areas of OSCC and cell lines of IHOK and OSCC under hypoxia, supporting hypoxia-aerobic glycolysis-acidosis axis. Expression of all proteins showed significant association with malignant conversion of OED and CA9 was an independent risk factor of malignant transformation of OED. But the predictability of malignant transformation was improved when all three proteins were applied together. CONCLUSION: High expression of CA9 was an independent predictive marker of malignant conversion. Moreover, the combined application of these three proteins may be useful to assess the risk of malignant conversion of OED.

[303]

TÍTULO / TITLE: - The antitumor lignan Nortrachelogenin sensitizes prostate cancer cells to TRAIL-induced cell death by inhibition of the Akt pathway and growth factor signaling.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Jun 6. pii: S0006-2952(13)00352-3. doi: 10.1016/j.bcp.2013.05.026.

●● Enlace al texto completo (gratis o de pago) 1016/j.bcp.2013.05.026

AUTORES / AUTHORS: - Peuhu E; Paul P; Remes M; Holmbom T; Eklund P; Sjöholm R; Eriksson JE

INSTITUCIÓN / INSTITUTION: - Turku Centre for Biotechnology, University of Turku and Abo Akademi University, Biocity, POB 123, FI-20521 Turku, Finland.

RESUMEN / SUMMARY: - Prostate cancer cells frequently develop resistance toward androgen-deprivation and chemotherapy. To identify new approaches to treat androgen-dependent prostate cancer, we have performed a structure-

activity analysis of lignan polyphenols for cancer cell specific sensitization to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a death ligand that has ability to induce tumor-specific cell death. In this study, we report that the lignan nortrachelogenin (NTG) is the most efficient of the 27 tested lignan compounds in sensitizing prostate cancer cells to TRAIL-induced apoptosis. Importantly, pretreatment with NTG does not sensitize a non-malignant prostate cell line to TRAIL-induced cell death. The structural comparison of lignans reveals that the dibenzylbutyrolactone skeleton is required for the apoptosis-sensitizing activity, while substitutions at the aromatic rings do not seem to play a critical role in this lignan function. Our study also characterizes the cellular effects and molecular mechanisms involved in NTG anticancer activity. We previously reported that specific lignans inhibit the Akt survival-signaling pathway in concert with TRAIL sensitization. While NTG is also shown to be an effective inhibitor of Akt signaling, in this study we further demonstrate that NTG potently inhibits tyrosine kinase (RTK) activation in response to growth factors, such as insulin and insulin-like growth factor I (IGF-I). Our results identify NTG as a novel agent for prostate cancer therapy with ability to inhibit Akt membrane localization and activity as well as the activation of growth factor receptors (GFRs), thereby efficiently synergizing with TRAIL exposure.

[304]

TÍTULO / TITLE: - Erratum to: Vascular endothelial growth factor receptors 1,3 and caveolin-1 are implicated in colorectal cancer aggressiveness and prognosis-correlations with epidermal growth factor receptor, CD44v6, focal adhesion kinase, and c-Met.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Aug;34(4):2119. doi: 10.1007/s13277-013-0918-5.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0918-5](#)

AUTORES / AUTHORS: - Garouniatis A; Zizi-Sermpetzoglou A; Rizos S; Kostakis A; Nikiteas N; Papavassiliou AG

INSTITUCIÓN / INSTITUTION: - Department of General Medicine, "G. Gennimatas" General Hospital, Athens, Greece.

[305]

TÍTULO / TITLE: - Belinostat-induced apoptosis and growth inhibition in pancreatic cancer cells involve activation of TAK1-AMPK signaling axis.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 19;437(1):1-6. doi: 10.1016/j.bbrc.2013.05.090. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.090](#)

AUTORES / AUTHORS: - Wang B; Wang XB; Chen LY; Huang L; Dong RZ

INSTITUCIÓN / INSTITUTION: - Department of Abdominal Surgical Oncology, Zhejiang Cancer Hospital, Hangzhou, Zhejiang 310022, China. Electronic address: wangbin69@yahoo.com.

RESUMEN / SUMMARY: - Pancreatic cancer accounts for more than 250,000 deaths worldwide each year. Recent studies have shown that belinostat, a novel pan histone deacetylases inhibitor (HDACi) induces apoptosis and growth inhibition in pancreatic cancer cells. However, the underlying mechanisms are not fully understood. In the current study, we found that AMP-activated protein kinase (AMPK) activation was required for belinostat-induced apoptosis and anti-proliferation in PANC-1 pancreatic cancer cells. A significant AMPK activation was induced by belinostat in PANC-1 cells. Inhibition of AMPK by RNAi knockdown or dominant negative (DN) mutation significantly inhibited belinostat-induced apoptosis in PANC-1 cells. Reversely, AMPK activator AICAR and A-769662 exerted strong cytotoxicity in PANC-1 cells. Belinostat promoted reactive oxygen species (ROS) production in PANC-1 cells, increased ROS induced transforming growth factor-beta-activating kinase 1 (TAK1)/AMPK association to activate AMPK. Meanwhile, anti-oxidants N-Acetyl-Cysteine (NAC) and MnTBAP as well as TAK1 shRNA knockdown suppressed belinostat-induced AMPK activation and PANC-1 cell apoptosis. In conclusion, we propose that belinostat-induced apoptosis and growth inhibition require the activation of ROS-TAK1-AMPK signaling axis in cultured pancreatic cancer cells.

[306]

TÍTULO / TITLE: - Role of the eIF4E binding protein 4E-BP1 in regulation of the sensitivity of human pancreatic cancer cells to TRAIL and celastrol-induced apoptosis.

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

REVISTA / JOURNAL: - Biol Cell. 2013 Jun 4. doi: 10.1111/boc.201300021.

●● [Enlace al texto completo \(gratis o de pago\) 1111/boc.201300021](#)

AUTORES / AUTHORS: - Chakravarthy R; Clemens MJ; Pirianov G; Perdios N; Mudan S; Cartwright JE; Elia A

INSTITUCIÓN / INSTITUTION: - Translational Control Group, Division of Biomedical Sciences, St George's, University of London, London, SW17 0RE, UK.

RESUMEN / SUMMARY: - BACKGROUND INFORMATION: Tumour cells can be induced to undergo apoptosis after treatment with the tumour necrosis factor alpha-related death-inducing ligand (TRAIL). Although human pancreatic cancer cells show varying degrees of response they can be sensitised to the pro-apoptotic effects of TRAIL in the presence of celastrol, a natural compound extracted from the plant *Tripterygium wilfordii* Hook F. One important aspect of the cellular response to TRAIL is the control of protein synthesis, a key regulator of which is the eukaryotic initiation factor 4E-binding protein, 4E-BP1.

RESULTS: We examined the effects of celastrol and TRAIL in several pancreatic cancer cell lines. In cells that are normally resistant to TRAIL, synergistic effects of TRAIL plus celastrol on commitment to apoptosis and inhibition of protein synthesis were observed. These were associated with a strong up-regulation and dephosphorylation of 4E-BP1. The enhancement of 4E-BP1 expression, which correlated with a threefold increase in the level of the 4E-BP1 transcript, was blocked by inhibitors of reactive oxygen species and the JNK protein kinase. When the expression of 4E-BP1 was reduced by an inducible micro-RNA, TRAIL-mediated apoptosis was inhibited. **CONCLUSION:** These results suggest that 4E-BP1 plays a critical role in the mechanism by which TRAIL and celastrol together cause apoptotic cell death in human pancreatic tumour cells.

[307]

TÍTULO / TITLE: - Cyclooxygenase-2 utilizes Jun N-terminal kinases to induce invasion, but not tamoxifen resistance, in MCF-7 breast cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 19. doi: 10.3892/or.2013.2549.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2549](#)

AUTORES / AUTHORS: - Gonzalez-Villasana V; Gutierrez-Puente Y; Tari AM

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Faculty of Biological Sciences, University of Nuevo Leon, San Nicolas de los Garza, Nuevo Leon, Mexico.

RESUMEN / SUMMARY: - Elevated cyclooxygenase-2 (COX-2) expression in breast tumors is associated with a lower survival rate in patients with estrogen receptor alpha (ERalpha)-positive tumors. We hypothesized that COX-2 reduces the survival rate of breast cancer patients with ERalpha-positive tumors since COX-2 increases the invasiveness of ERalpha-positive breast tumors and decreases tumor sensitivity to tamoxifen. Previously, we demonstrated that COX-2 stimulates the activity of protein kinase C (PKC) to increase the invasiveness of ERalpha-positive MCF-7 breast cancer cells and to decrease the sensitivity of MCF-7 cells to tamoxifen. High levels of COX-2 are associated with the activation of the mitogen-activated protein kinase (MAPK) family and the Akt kinase. However, it is not known whether these kinases mediate COX-2-induced invasive activity and tamoxifen resistance. In the present study, we report that COX-2 utilizes PKC to enhance the phosphorylation of Jun N-terminal kinases (JNKs), but not that of other MAPK family members or Akt. Inhibition aimed at JNKs reduced COX-2-induced invasion but not COX-2-induced tamoxifen resistance. We conclude that JNKs are essential for induced cell invasion by COX-2, but not tamoxifen resistance, in ERalpha-positive breast cancer cells.

[308]

TÍTULO / TITLE: - Carbon anhydrase IX specific immune responses in patients with metastatic renal cell carcinoma potentially cured by interleukin-2 based immunotherapy.

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

REVISTA / JOURNAL: - Immunopharmacol Immunotoxicol. 2013 Aug;35(4):487-96. doi: 10.3109/08923973.2013.802802. Epub 2013 Jun 27.

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

[3109/08923973.2013.802802](#)

AUTORES / AUTHORS: - Rasmussen S; Donskov F; Pedersen JW; Wandall HH; Buus S; Harndahl M; Braendstrup P; Claesson MH; Pedersen AE

INSTITUCIÓN / INSTITUTION: - Department of International Health, Immunology and Microbiology, The Faculty of Health and Medical Sciences, University of Copenhagen , Denmark .

RESUMEN / SUMMARY: - Abstract The majority of clear-cell renal cell carcinomas (ccRCC) show high and homogeneous expression levels of the tumor associated antigen (TAA) carbonic anhydrase IX (CAIX), and treatment with interleukin-2 (IL-2) based immunotherapy can lead to cure in patients with metastatic renal cell carcinoma (mRCC). However, the involvement of CAIX specific CD8+ T cells and/or NK cells in the tumor eradication is unknown. We investigated T cell and antibody reactivity against overlapping 15-mer CAIX-peptides as well as HLA haplotype frequency and NK cell cytotoxicity in 11 patients with no evidence of disease (NED) following treatment with IL-2 based immunotherapy, and thus potentially cured. Immune reactivity in these patients was compared with samples from patients with dramatic tumor response obtained immediately at the cessation of therapy, samples from patients that experienced progressive disease during treatment and samples from healthy controls. We observed more focused but only weak and not consistent CAIX specific T-cells in the late observation and early observation response groups compared with the healthy control group. An increased frequency of the class II alleles HLA-DRB4 01:01, HLA-DPB 01:01 and HLA-DPB 03:01 was noted in the NED patients. In contrast, NK cytotoxicity was low even in the late observation response group as compared with controls. In particular, a HLA-B*40:01 restricted CD8+ T cell response recognizing the CAIX-derived peptide SEEEGSLKL was identified. This may have interest in future cancer vaccines, but more studies are needed to elucidate the immunological mechanisms of action in potentially cured patients treated with an immunotherapeutic agent.

[309]

TÍTULO / TITLE: - SNAI1 Protein Expression is an Independent Negative Prognosticator in Muscle-Invasive Bladder Cancer.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 27.

- Enlace al texto completo (gratis o de pago) [1245/s10434-013-3075-](https://doi.org/10.1245/s10434-013-3075-6)

[6](#)

AUTORES / AUTHORS: - Keck B; Wach S; Goebell PJ; Kunath F; Bertz S; Lehmann J; Stockle M; Taubert H; Wullich B; Hartmann A

INSTITUCIÓN / INSTITUTION: - Department of Urology, University Hospital Erlangen, Erlangen, Germany, bastian.keck@uk-erlangen.de.

RESUMEN / SUMMARY: - **BACKGROUND:** The prognosis of muscle-invasive bladder cancer is poor. Molecular prognosticators have gained increasing attention for individualized therapeutic options because they can identify patients with different prognoses. **METHODS:** Tissue microarrays of formalin-fixed and paraffin-embedded tumor samples from 206 bladder cancer patients treated with cystectomy and chemotherapy were studied for SNAI1 protein expression by immunohistochemistry. SNAI1 expression was evaluated using an immunoreactive score (IRS). For statistical analysis, the patients were separated into two groups: those with tumor specimens negative for SNAI1 expression (IRS = 0), and the other positive for SNAI1 expression (IRS \geq 1). **RESULTS:** Tumor samples from 42 patients showed negative SNAI1 expression, whereas the nuclei of tumor cells from 164 patients showed detectable nuclear staining of SNAI1. A Kaplan-Meier analysis of the bladder cancer patients with negative SNAI1 expression showed significantly reduced disease-specific survival (DSS) and progression-free survival (PFS) compared to the patients with positive expression ($p = 0.010$ and 0.013). A multivariate Cox regression analysis (adjusted for gender, age, tumor stage, tumor grade, lymph node metastasis, chemotherapy, and histologic subtype) again showed a significant correlation between patients lacking SNAI1 expression and DSS ($p = 0.005$; relative risk 2.31; 95 % confidence interval 1.28-4.17) or PFS ($p = 0.004$; relative risk 2.20; 95 % confidence interval 1.29-3.78) compared to patients with positive SNAI1 staining. **CONCLUSIONS:** Loss of SNAI1 protein expression is an independent prognosticator for PFS and DSS in bladder cancer patients treated by radical cystectomy and adjuvant chemotherapy. Its prognostic value for neoadjuvant or adjuvant chemotherapy must be evaluated in further prospective randomized controlled trials.

[310]

TÍTULO / TITLE: - Breast cancer subtyping by immunohistochemistry and histological grade outperforms breast cancer intrinsic subtypes in predicting neoadjuvant chemotherapy response.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jul;140(1):63-71. doi: 10.1007/s10549-013-2620-0. Epub 2013 Jul 5.

- Enlace al texto completo (gratis o de pago) [1007/s10549-013-2620-](https://doi.org/10.1007/s10549-013-2620-0)

[0](#)

AUTORES / AUTHORS: - Lips EH; Mulder L; de Ronde JJ; Mandjes IA; Koolen BB; Wessels LF; Rodenhuis S; Wesseling J

INSTITUCIÓN / INSTITUTION: - Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.

RESUMEN / SUMMARY: - Intrinsic subtypes are widely accepted for the classification of breast cancer. Lacking gene expression data, surrogate classifications based on immunohistochemistry (IHC) have been proposed. A recent St. Gallen consensus meeting recommends to use this “surrogate intrinsic subtypes” for predicting adjuvant chemotherapy resistance, implying that “Surrogate Luminal A” breast cancers should only receive endocrine therapy. In this study we assessed both gene expression based intrinsic subtypes as well as surrogate intrinsic subtypes regarding their power to predict neoadjuvant chemotherapy benefit. Single institution data of 560 breast cancer patients were reviewed. Gene expression data was available for 247 patients. Subtypes were determined on the basis of IHC, Ki67, histological grade, endocrine responsiveness, and gene expression, and were correlated with chemotherapy response and recurrence-free survival. In ER+/HER2- tumors, a high histological grade was the best predictor for chemotherapy benefit, both in terms of pCR ($p = 0.004$) and recurrence-free survival ($p = 0.002$). The gene expression based and surrogate intrinsic subtype based on Ki67 had no predictive or prognostic value in ER+/HER2- tumors. Histological grade, ER, PR, and HER2 were the best predictive factors for chemotherapy response in breast cancer. We propose to continue the conventional use of these markers.

[311]

TÍTULO / TITLE: - Activity of gefitinib in a non-small-cell lung cancer patient with both activating and resistance EGFR mutations.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Jul;8(7):e59-60. doi: 10.1097/JTO.0b013e318286cc26.

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

[1097/JTO.0b013e318286cc26](#)

AUTORES / AUTHORS: - Morabito A; Costanzo R; Rachiglio AM; Pasquale R; Sandomenico C; Franco R; Montanino A; De Lutio E; Rocco G; Normanno N

INSTITUCIÓN / INSTITUTION: - Medical Oncology Unit, Thoraco-Pulmonary Department, National Cancer Institute, Napoli, Italy.

alessandromorabito1@virgilio.it

[312]

TÍTULO / TITLE: - Tumor suppressor gene Oxidored-nitro domain-containing protein 1 regulates nasopharyngeal cancer cell autophagy, metabolism, and apoptosis in vitro.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Jul 3;45(9):2016-2026. doi: 10.1016/j.biocel.2013.06.020.

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

[1016/j.biocel.2013.06.020](#)

AUTORES / AUTHORS: - Li W; Li X; Wang W; Yi M; Zhou Y; Zheng P; Xiong W; Yang J; Peng S; McCarthy JB; Xiang B; Li G

INSTITUCIÓN / INSTITUTION: - Hunan Provincial Tumor Hospital and the Affiliated Tumor Hospital of Xiangya School of Medicine, Central South University, Changsha 410013, Hunan, China; Key Laboratory of Carcinogenesis of Ministry of Health and Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Cancer Research Institute, Central South University, Changsha 410078, Hunan, China.

RESUMEN / SUMMARY: - Autophagy is a cellular survival mechanism that involves the catabolic degradation of damaged proteins and organelles during stress. It is particularly required for tumor cell survival during starvation and tumorigenesis. NOR1 is a putative tumor suppressor gene. This study investigated in vitro the effects of NOR1 on the regulation of nasopharyngeal carcinoma autophagy, metabolism, and apoptosis. The data showed that acute oxidative stress induced the expression of NOR1 in normal human cells and tumor cells. Restoration of NOR1 expression downregulated basal autophagy, assessed by autophagy marker LC3 conversion and transmission electron microscopy. In NOR1-expressing tumor cells, reduced autophagy inhibited mitochondrial respiration and energy metabolism. Restoration of NOR1 expression in nasopharyngeal carcinoma cells enhanced apoptosis after induction of oxidative stress. NOR1 expression upregulated Bax expression, Bax translocation to the mitochondria, Smac/DIABLO release from the mitochondria, and activation of caspase-9, and -3, and PARP. In contrast, knockdown of NOR1 expression using NOR1 RNAi resulted in an increase in autophagy and attenuated hydrogen peroxide-induced cell death in HeLa cells. In addition, expression of NOR1 significantly inhibited cisplatin-induced autophagy, resulting in increased cisplatin cytotoxicity and apoptosis. These data revealed novel aspects of the interplay between autophagy and apoptosis in nasopharyngeal carcinoma cells, which underlies the tumor suppression function of NOR1. This work may provide novel insights to contribute to the development of a combinatorial therapy for nasopharyngeal carcinoma.

[313]

TÍTULO / TITLE: - MET overexpression assessed by new interpretation method predicts gene amplification and poor survival in advanced gastric carcinomas.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Jun 28. doi: 10.1038/modpathol.2013.108.

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

[1038/modpathol.2013.108](#)

AUTORES / AUTHORS: - Ha SY; Lee J; Kang SY; Do IG; Ahn S; Park JO; Kang WK; Choi MG; Sohn TS; Bae JM; Kim S; Kim M; Kim S; Park CK; Ignatius Ou SH; Kim KM

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - The establishment of better selection criteria for identifying sub-populations that may benefit from treatment is a key aspect of the development and success of targeted therapy. To investigate methods for assessing MET overexpression in gastric cancer, we conducted immunohistochemistry using a new anti-Total MET monoclonal antibody in a single-institution cohort of 495 patients. As antibody is directed against a membranous and/or cytoplasmic epitope, two interpretation methods were used: (1) membranous and cytoplasmic and (2) membranous alone. In selected 120 cases, copy number gain and mRNA expression levels were measured using quantitative real-time PCR. Further in situ hybridization confirmed the presence of MET gene amplification. Among the 495 gastric cancers, simultaneous membranous and cytoplasmic overexpression of MET was found in 108 cases (21.8%) and membranous alone overexpression was observed in 40 cases (8.1%). The highest correlation was observed in membranous and cytoplasmic staining of MET: MET expression scores correlated significantly with high MET mRNA levels ($r=0.465$, $P<0.0001$), increased copy number gain ($r=0.393$, $P=0.000002$) and amplification of MET gene. Moreover, patients with MET overexpression showed shorter overall survival (HR, 1.781; 95% CI, 1.324-2.395; $P<0.001$) and disease-free survival (HR, 1.765; 95% CI, 1.227-2.541; $P=0.002$) compared with patients without MET overexpression. However, membranous overexpression of MET did not highly correlate with mRNA level ($r=0.274$, $P=0.002$), copy number gain or survival ($P>0.05$). We developed highly correlating interpretation methods of MET immunohistochemistry in gastric carcinomas. MET overexpression is an independent prognostic factor and could be a potential target and predictor of benefit for targeted therapy with MET inhibitors. Modern Pathology advance online publication, 28 June 2013; doi:10.1038/modpathol.2013.108.

[314]

TÍTULO / TITLE: - Genome-wide transcriptional analysis of apoptosis-related genes and pathways regulated by H2AX in lung cancer A549 cells.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Sep;18(9):1039-47. doi: 10.1007/s10495-013-0875-x.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0875-](http://1007/s10495-013-0875-x)

[X](#)

AUTORES / AUTHORS: - Lu C; Xiong M; Luo Y; Li J; Zhang Y; Dong Y; Zhu Y; Niu T; Wang Z; Duan L

INSTITUCIÓN / INSTITUTION: - Aviation Medicine Research Laboratory, Air Force General Hospital, PLA, Beijing, 100142, China, luchengrong@263.net.

RESUMEN / SUMMARY: - Histone H2AX is a novel tumor suppressor protein and plays an important role in apoptosis of cancer cells. However, the role of H2AX in lung cancer cells is unclear. The detailed mechanism and epigenetic regulation by H2AX remain elusive in cancer cells. We showed that H2AX was involved in apoptosis of lung cancer A549 cells as in other tumor cells. Knockdown of H2AX strongly suppressed apoptosis of A549 cells. We clarified the molecular mechanisms of apoptosis regulated by H2AX based on genome-wide transcriptional analysis. Microarray data analysis demonstrated that H2AX knockdown in A549 cells affected expression of 3,461 genes, including upregulation of 1,435 and downregulation of 2,026. These differentially expressed genes were subjected to bioinformatic analysis for exploring biological processes regulated by H2AX in lung cancer cells. Gene ontology analysis showed that H2AX affected expression of many genes, through which, many important functions including response to stimuli, gene expression, and apoptosis were involved in apoptotic regulation of lung cancer cells. Pathway analysis identified the mitogen-activated protein kinase signaling pathway and apoptosis as the most important pathways targeted by H2AX. Signal transduction pathway networks analysis and chromatin immunoprecipitation assay showed that two core genes, NFKB1 and JUN, were involved in apoptosis regulated by H2AX in lung cancer cells. Taken together, these data provide compelling clues for further exploration of H2AX function in cancer cells.

[315]

TÍTULO / TITLE: - Gene expression-based prediction of myeloma cell sensitivity to histone deacetylase inhibitors.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 6;109(3):676-85. doi: 10.1038/bjc.2013.392. Epub 2013 Jul 18.

●● Enlace al texto completo (gratis o de pago) 1038/bjc.2013.392

AUTORES / AUTHORS: - Moreaux J; Reme T; Leonard W; Veyrone JL; Requirand G; Goldschmidt H; Hose D; Klein B

INSTITUCIÓN / INSTITUTION: - 1] CHU Montpellier, Institute of Research in Biotherapy, Montpellier, France [2] INSERM-UM1 U1040, Institute for Research in Biotherapy, CHU Montpellier, Av Augustin Fliche, Montpellier 34197, France.

RESUMEN / SUMMARY: - Background: Multiple myeloma (MM) is still a fatal plasma cell cancer. Novel compounds are currently clinically tested as a single agent in relapsing patients, but in best cases with partial response of a fraction of patients, emphasizing the need to design tools predicting drug efficacy. Histone deacetylase inhibitors (HDACi) are anticancer agents targeting epigenetic regulation of gene expression and are in clinical development in MM. Methods: To create a score predicting HDACi efficacy, five MM cell lines were treated with trichostatin A (TSA) and gene expression profiles were determined. Results: The expression of 95 genes was found to be upregulated by TSA, using paired supervised analysis with Significance Analysis of Microarrays software. Thirty-seven of these 95 genes had prognostic value for overall survival in a cohort of 206 newly diagnosed MM patients and their prognostic information was summed up in a histone acetylation score (HA Score); patients with the highest HA Score had the shorter overall survival. It is worth noting that MM cell lines or patients' primary MM cells with a high HA Score had a significant higher sensitivity to TSA, valproic acid, panobinostat or vorinostat. Conclusion: In conclusion, the HA Score allows identification of MM patients with poor survival, who could benefit from HDACi treatment.

[316]

TÍTULO / TITLE: - Doxorubicin induces atypical NF-kappaB activation through c-Abl kinase activity in breast cancer cells.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1476-](#)

[3](#)

AUTORES / AUTHORS: - Esparza-Lopez J; Medina-Franco H; Escobar-Arriaga E; Leon-Rodriguez E; Zentella-Dehesa A; Ibarra-Sanchez MJ

INSTITUCIÓN / INSTITUTION: - Unidad de Bioquímica, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubiran", Vasco de Quiroga 15, Sección XVI, Delegación Tlalpan, CP 14000, México, DF, México.

RESUMEN / SUMMARY: - PURPOSE: NF-kappaB transcription factor has been associated with cancer development and chemoresistance. We studied the signaling pathway activated by doxorubicin (DOX) leading to NF-kappaB activation in breast cancer cells. METHODS: NF-kappaB activity was evaluated by electrophoretic mobility shift in T47D, ZR75.30 and primary culture (MBCDF) from a ductal infiltrating carcinoma. Cell viability was measured by crystal violet. Western blotting was performed to check the expression and phosphorylation of I kappa B alpha Ser-32/36. c-Abl was inhibited with Imatinib or by overexpressing a dominant negative form of c-Abl (K290R). RESULTS: We found a correlation between sensitivity to DOX and amplitude of NF-kappaB activation. In cells least sensitive to DOX, NF-kappaB remained activated for longer time (T47D and MBCDF). The opposite effect was observed in cells

sensitive to DOX (ZR75.30). DOX did not induce I κ B degradation or Ser-32/36 phosphorylation. Instead, there were modifications in the levels of I κ B tyrosine phosphorylation, suggesting an atypical NF- κ B activation. In DOX-resistant cells, Imatinib treatment reduced I κ B tyrosine phosphorylation and NF- κ B activity. The Imatinib-DOX combination significantly enhanced cell death of T47D and MBCDF breast cancer cells. Overexpression of c-Abl K290R in T47D and MBCDF cells reduced basal and DOX-induced NF- κ B activation as well as I κ B tyrosine phosphorylation. In c-Abl K290R cells, DOX treatment did not mimic the combination Imatinib-DOX-induced cell death. CONCLUSIONS: Inhibition of c-Abl inactivated I κ B/NF- κ B pathway is associated with I κ B tyrosine phosphorylation in breast cancer cells. These results also raise the potential use of a combined therapy with Imatinib and DOX for breast cancer patients.

[317]

TÍTULO / TITLE: - CXI-benzo-84 reversibly binds to tubulin at colchicine site and induces apoptosis in cancer cells.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Aug 1;86(3):378-91. doi: 10.1016/j.bcp.2013.05.024. Epub 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1016/j.bcp.2013.05.024](#)

AUTORES / AUTHORS: - Rai A; Gupta TK; Kini S; Kunwar A; Surolia A; Panda D

INSTITUCIÓN / INSTITUTION: - Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India.

RESUMEN / SUMMARY: - Here, we have discovered CXI-benzo-84 as a potential anticancer agent from a library of benzimidazole derivatives using cell based screening strategy. CXI-benzo-84 inhibited cell cycle progression in metaphase stage of mitosis and accumulated spindle assembly checkpoint proteins Mad2 and BubR1 on kinetochores, which subsequently activated apoptotic cell death in cancer cells. CXI-benzo-84 depolymerized both interphase and mitotic microtubules, perturbed EB1 binding to microtubules and inhibited the assembly and GTPase activity of tubulin in vitro. CXI-benzo-84 bound to tubulin at a single binding site with a dissociation constant of $1.2 \pm 0.2 \mu\text{M}$. Competition experiments and molecular docking suggested that CXI-benzo-84 binds to tubulin at the colchicine-site. Further, computational analysis provided a significant insight on the binding site of CXI-benzo-84 on tubulin. In addition to its potential use in cancer chemotherapy, CXI-benzo-84 may also be useful to screen colchicine-site agents and to understand the colchicine binding site on tubulin.

[318]

TÍTULO / TITLE: - A diverse induction of apoptosis by trabectedin in MCF-7 (HER2-/ER+) and MDA-MB-453 (HER2+/ER-) breast cancer cells.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Jun 20;221(2):128-136. doi: 10.1016/j.toxlet.2013.06.213.

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

1016/j.toxlet.2013.06.213

AUTORES / AUTHORS: - Atmaca H; Bozkurt E; Uzunoglu S; Uslu R; Karaca B

INSTITUCIÓN / INSTITUTION: - Section of Molecular Biology, Department of Biology, Faculty of Science and Letters, Celal Bayar University, 45140 Muradiye, Manisa, Turkey. Electronic address: harika.atmaca@cbu.edu.tr.

RESUMEN / SUMMARY: - Trabectedin (Yondelis, ET-743), a semi synthetic tetrahydroisoquinoline alkaloid that was originally derived from the marine tunicate Ecteinascidia turbinata. The objective of this study was to investigate whether trabectedin mediated apoptosis shows any diversity in human breast cancer cell lines with different genotypes. Trabectedin induced cytotoxicity and apoptosis in both breast cancer cells in a time and concentration-dependent manner. The expression levels of the death receptor pathway molecules, TRAIL-R1/DR4, TRAIL-R2/DR5, FAS/TNFRSF6, TNF RI/TNFRSF1A, and FADD were significantly increased by 2.6-, 3.1-, 1.7-, 11.2- and 4.0-fold by trabectedin treatment in MCF-7 cells. However, in MDA-MB-453 cells, the mitochondrial pathway related pro-apoptotic proteins Bax, Bad, Cytochrome c, Smac/DIABLO, and Cleaved Caspase-3 expressions were induced by 4.2-, 3.6-, 4.8-, 4.5-, and 4.4-fold, and the expression levels of anti-apoptotic proteins Bcl-2 and Bcl-XL were reduced by 4.8- and 5.2-fold in MDA-MB-453 cells. Moreover, trabectedin treatment increased the generation of ROS in both breast cancer cells. We have shown that trabectedin causes selective activation of extrinsic and intrinsic apoptotic pathways in two genotypically different breast cancer cells. This preliminary data might guide clinicians to choose appropriate combination agents with trabectedin based on different molecular subtypes of breast cancer.

[319]

TÍTULO / TITLE: - Treating Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors.

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

REVISTA / JOURNAL: - Acta Haematol. 2013 Jun 13;130(3):192-195.

●● Enlace al texto completo (gratis o de pago) [1159/000351957](https://doi.org/10.1159/000351957)

AUTORES / AUTHORS: - Gale RP; Goldman JM

INSTITUCIÓN / INSTITUTION: - Section of Haematology, Division of Experimental Medicine, Department of Medicine, Imperial College, London, UK.

[320]

TÍTULO / TITLE: - Apoptosis induced by PGC-1beta in breast cancer cells is mediated by the mTOR pathway.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 18. doi: 10.3892/or.2013.2628.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2628](#)

AUTORES / AUTHORS: - Wang L; Liu Q; Li F; Qiu J; Fan H; Ma H; Zhu Y; Wu L; Han X; Yang Z; Jiang H; Wei J; Xia H

INSTITUCIÓN / INSTITUTION: - Life Science College, Shaanxi Normal University, Xi'an 710062, P.R. China.

RESUMEN / SUMMARY: - The peroxisome proliferator-activated receptor-gamma (PPAR-gamma) coactivator-1beta (PGC-1beta) is a well-established regulator of mitochondrial biogenesis. However, the underlying mechanism of PGC-1beta action remains elusive. This study reveals that knockdown of endogenous PGC-1beta by short-hairpin RNA (shRNA) leads to a decrease in the expression of mammalian target of rapamycin (mTOR) pathway-related genes in MDA-MB-231 cells. After knockdown of PGC-1beta, phosphorylation of AMP-activated protein kinase (AMPK), phosphorylation of Rictor on Thr1135, Raptor and S6 protein was inhibited. However, Akt phosphorylation on Ser473 was upregulated and cell apoptosis occurred. In particular, we demonstrate that the levels of PGC-1beta and mTOR correlated with overall mitochondrial activity. These results provide new evidence that cell apoptosis is orchestrated by the balance between several signaling pathways, and that PGC-1beta takes part in these events in breast cancer cells mediated by the mTOR signaling pathway.

[321]

TÍTULO / TITLE: - Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAFety Assessment of Biologic ThERapy (SABER) Study.

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

REVISTA / JOURNAL: - Ann Rheum Dis. 2013 Jul 13. doi: 10.1136/annrheumdis-2013-203407.

●● Enlace al texto completo (gratis o de pago) [1136/annrheumdis-2013-203407](#)

AUTORES / AUTHORS: - Baddley JW; Winthrop KL; Chen L; Liu L; Grijalva CG; Delzell E; Beukelman T; Patkar NM; Xie F; Saag KG; Herrinton LJ; Solomon DH; Lewis JD; Curtis JR

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA.

RESUMEN / SUMMARY: - OBJECTIVES: To determine among patients with autoimmune diseases in the USA whether the risk of non-viral opportunistic infections (OI) was increased among new users of tumour necrosis factor alpha inhibitors (TNFI), when compared to users of non-biological agents used for

active disease. METHODS: We identified new users of TNFI among cohorts of rheumatoid arthritis (RA), inflammatory bowel disease and psoriasis-psoriatic arthritis-ankylosing spondylitis patients during 1998-2007 using combined data from Kaiser Permanente Northern California, two pharmaceutical assistance programmes for the elderly, Tennessee Medicaid and US Medicaid/Medicare programmes. We compared incidence of non-viral OI among new TNFI users and patients initiating non-biological disease-modifying antirheumatic drugs (DMARD) overall and within each disease cohort. Cox regression models were used to compare propensity-score and steroid- adjusted OI incidence between new TNFI and non-biological DMARD users. RESULTS: Within a cohort of 33 324 new TNFI users we identified 80 non-viral OI, the most common of which was pneumocystosis (n=16). In the combined cohort, crude rates of non-viral OI among new users of TNFI compared to those initiating non-biological DMARD was 2.7 versus 1.7 per 1000-person-years (aHR 1.6, 95% CI 1.0 to 2.6). Baseline corticosteroid use was associated with non-viral OI (aHR 2.5, 95% CI 1.5 to 4.0). In the RA cohort, rates of non-viral OI among new users of infliximab were higher when compared to patients newly starting non-biological DMARD (aHR 2.6, 95% CI 1.2 to 5.6) or new etanercept users (aHR 2.9, 95% CI 1.5 to 5.4). CONCLUSIONS: In the USA, the rate of non-viral OI was higher among new users of TNFI with autoimmune diseases compared to non-biological DMARD users.

[322]

TÍTULO / TITLE: - Clinical implications of fibroblast activation protein-alpha in non-small cell lung cancer after curative resection: a new predictor for prognosis.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1471-](#)

[8](#)

AUTORES / AUTHORS: - Liao Y; Ni Y; He R; Liu W; Du J

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan, 250021, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: Fibroblast activation protein-alpha (FAP-alpha), which is a serine protease specially expressed on the surface of the cancer stromal cells, plays an important role in the progression and prognosis in diverse malignancies. However, the role of FAP-alpha in non-small cell lung cancer (NSCLC) is still unknown. MATERIALS AND METHODS: We enrolled 59 NSCLC patients who received complete resection. Sections of paraffin-embedded primary NSCLC specimens of all the patients were stained with antibody directed against FAP-alpha. Overall, percentage (Grade 0-3) and intensity (0-3+) of stromal FAP-alpha staining of the tumor were assessed.

RESULTS: FAP-alpha was detected in >76 % of the specimens examined, and its high expression seemed to be correlated with poor tumor differentiation (P = 0.06). Furthermore, both increased FAP-alpha staining percentage and intensity were associated with worse overall survival of the patients (percentage, P = 0.0087; intensity, P = 0.05). Higher FAP-alpha staining percentage was observed in those patients with increased peripheral neutrophil and lymphocyte count ratio (P = 0.034). CONCLUSIONS: FAP-alpha is highly expressed in cancer stroma and also a predictor of poor survival of NSCLC patients. Elevated FAP-alpha expression may be associated with inflammation and suppressed lymphocyte-dependent immune response, which then result in the tumor progression. Therefore, FAP-alpha plays an important role in the progression of NSCLC, and its high expression is a predictor of poor survival. Targeting FAP-alpha may be a novel strategy for NSCLC therapy.

[323]

TÍTULO / TITLE: - Enhancer of Zeste Homolog 2 (EZH2) Promotes Progression of Cholangiocarcinoma Cells by Regulating Cell Cycle and Apoptosis.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3135-](#)

[y](#)

AUTORES / AUTHORS: - Nakagawa S; Okabe H; Sakamoto Y; Hayashi H; Hashimoto D; Yokoyama N; Sakamoto K; Kuroki H; Mima K; Nitta H; Imai K; Chikamoto A; Watanabe M; Beppu T; Baba H

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the polycomb repressive complex 2 (PRC2). When present in PRC2, EZH2 catalyzes trimethylation on lysine 27 residue of histone H3, resulting in epigenetic silencing of gene expression and cancer progression. We investigated the expression and function of EZH2 in intrahepatic and extrahepatic cholangiocarcinoma (ICC and ECC). METHODS: The influence of EZH2 on cell growth and apoptosis was assessed by knockdown experiments. Target gene of EZH2 was searched by quantitative RT-PCR. Clinical significance of EZH2 in 86 cholangiocarcinoma patients (45 ICC and 41 ECC) who underwent curative surgery was examined by immunohistochemistry. RESULTS: In vitro analysis, knockdown of EZH2 reduced cell growth, induced G1 arrest, and induced apoptosis, as confirmed by Annexin V staining and increased sub-G1 populations in cholangiocarcinoma cell lines. The expression levels of p16 INK4a and p27 KIP1 were remarkably increased by knockdown of EZH2 in these cell lines. In immunohistochemical study, EZH2 upregulation correlated with tumor diameter (p = 0.0103) in ICC, lymph node metastasis (p = 0.0292) in ECC, and Ki67 index in both ICC (p = 0.0364) and ECC (p = 0.0017).

In addition, EZH2 expression was correlated with poor prognosis in both ICC ($p = 0.0447$) and ECC ($p = 0.0227$). CONCLUSIONS: The current study demonstrated relationships between EZH2 expression and acceleration of the cell cycle and antiapoptosis, and poor prognosis in cholangiocarcinoma. These results suggest that EZH2 may represent a potential therapeutic target in patients with cholangiocarcinoma.

[324]

TÍTULO / TITLE: - Tamoxifen therapy in breast cancer: do apolipoprotein E genotype and menopausal state affect plasma lipid changes induced by the drug?

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

REVISTA / JOURNAL: - Int J Biol Markers. 2013 Jun 26:0. doi: 10.5301/jbm.5000037.

●● Enlace al texto completo (gratis o de pago) [5301/jbm.5000037](#)

AUTORES / AUTHORS: - Alonso MG; Gomez-Chacon GF; Lorca AR; Villajos AN; Gomez AT; Moya FB; Santander AF

INSTITUCIÓN / INSTITUTION: - Department of Basic Biomedical Sciences, Faculty of Biomedical Sciences, Universidad Europea de Madrid, Madrid - España.

RESUMEN / SUMMARY: - Objective: This study examines the lipid profile change produced in response to tamoxifen (TAM) treatment, and its possible relationship with both apolipoprotein E genotype and menopausal state in patients with breast cancer. Methods: Blood samples were collected from 86 Spanish women with breast cancer before initiating TAM treatment and in the following 6, 12 and 18 months of treatment. Plasma lipid levels (total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol) were determined using an automatic analyzer. Genotypes for apolipoprotein E (ApoE) were identified by PCR-RFLP using the HhaI enzyme. Results: In all patients, significant reductions in total cholesterol and LDL-cholesterol concentrations and a significant increase in triglyceride concentrations were observed after 6, 12, and 18 months of TAM treatment compared to baseline ($p < 0.01$ for each time point). In the subset of APOE4-negative patients, triglyceride concentrations also significantly increased after 6, 12, and 18 months of treatment ($p = 0.019$, $p = 0.045$, $p = 0.001$, respectively), while APOE4-positive patients showed no significant lipid changes at 12 and 18 months. However, after 18 months of TAM treatment the overall triglyceride concentrations had risen by 24.75% in APOE4-negative patients vs 29.9% in APOE4-positive patients. In postmenopausal women, significant reductions in total cholesterol, LDL-cholesterol and LDL/HDL ratios were observed at each time point ($p < 0.020$ for each). Conclusions: TAM treatment induced similar plasma triglyceride increases in patients with positive or negative APOE genotype. Compared to premenopausal patients, postmenopausal breast

cancer patients showed a more beneficial lipid profile change in response to treatment.

[325]

TÍTULO / TITLE: - Zn induces apoptosis in human highly metastatic SHG-44 glioma cells, through inhibiting activity of the voltage-gated proton channel Hv1.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 24. pii: S0006-291X(13)01227-8. doi: 10.1016/j.bbrc.2013.07.067.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.07.067

AUTORES / AUTHORS: - Wang Y; Zhang S; Li SJ

INSTITUCIÓN / INSTITUTION: - Department of Biophysics, School of Physics Science, Nankai University, Tianjin 300071, China.

RESUMEN / SUMMARY: - In contrast to the voltage-gated K⁺ channels, the voltage-gated proton channel Hv1 contains a voltage-sensor domain but lacks a pore domain. Here, we showed that Hv1 is expressed in the highly metastatic glioma cell SHG-44, but lowly in the poorly metastatic glioma cell U-251. Inhibition of Hv1 activity by 140μM zinc chloride induces apoptosis in the human highly metastatic glioma cells. Zn²⁺ ions markedly inhibit proton secretion, and reduce the gelatinase activity in the highly metastatic glioma cells. In vivo, the glioma tumor sizes of the implantation of the SHG-44 xenografts in nude mice that were injected zinc chloride solution, were dramatically smaller than that in the controlled groups. The results demonstrated that the inhibition of Hv1 activity via Zn²⁺ ions can effectively retard the cancer growth and suppress the cancer metastasis by the decrease of proton extrusion and the down-regulation of gelatinase activity. Our results suggest that Zn²⁺ ions may be used as a potential anti-glioma drug for glioma therapy.

[326]

TÍTULO / TITLE: - Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jun 11;108(11):2259-63. doi: 10.1038/bjc.2013.255. Epub 2013 May 30.

●● Enlace al texto completo (gratis o de pago) 1038/bjc.2013.255

AUTORES / AUTHORS: - Zagouri F; Sergentanis TN; Koutoulidis V; Sparber C; Steger GG; Dubsky P; Zografos GC; Psaltopoulou T; Gnant M; Dimopoulos MA; Bartsch R

INSTITUCIÓN / INSTITUTION: - Department of Medicine I/Division of Oncology, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria. florazagouri@yahoo.co.uk

RESUMEN / SUMMARY: - BACKGROUND: Data regarding the safety and effectiveness of aromatase inhibitors (AIs) as monotherapy or combined with gonadotropin-releasing hormone (GnRH) analogue in male breast cancer are scarce. METHODS: In this retrospective chart review, cases of male breast cancer patients treated with AIs with or without a GnRH analogue were evaluated. RESULTS: Twenty-three men were included into this case series. Aromatase inhibitors in combination with or without a GnRH analogue were given as first-line therapy in 60.9% and as second-line therapy in 39.1% of patients, respectively. All patients had visceral metastases, whereas in five of them bone lesions coexisted. In all cases AIs were tolerated well, and no case of grade 3 and 4 adverse events was reported. A partial response was observed in 26.1% of patients and stable disease in 56.5%. Median overall survival (OS) was 39 months and median progression-free survival (PFS) was 13 months. Regarding OS and PFS, no significant effects of GnRH analogue co-administration or type of AI were noted. CONCLUSION: Our study shows that AIs with or without GnRH analogues may represent an effective and safe treatment option for hormone-receptor positive, pretreated, metastatic, male breast cancer patients.

[327]

TÍTULO / TITLE: - Curcumin induces cell cycle arrest and apoptosis of prostate cancer cells by regulating the expression of I κ B α , c-Jun and androgen receptor.

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

REVISTA / JOURNAL: - Pharmazie. 2013 Jun;68(6):431-4.

AUTORES / AUTHORS: - Guo H; Xu YM; Ye ZQ; Yu JH; Hu XY

INSTITUCIÓN / INSTITUTION: - Department of Urology, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China.

RESUMEN / SUMMARY: - Curcumin possesses chemopreventive properties against several types of cancer, but the molecular mechanisms by which it induces apoptosis of cancer cells and inhibits cancer cell proliferation are not clearly understood. To evaluate the antitumor activity of curcumin for prostate cancer, we used an androgen dependent LNCaP prostate cancer cell line and an androgen independent PC-3 prostate cancer cell line as experimental models. We treated these cells with curcumin and then evaluated the effects of curcumin on cell cycle profiling and apoptosis, as well as the activation of NF- κ B and c-jun in these cells. The results showed that the ratios of apoptosis in LNCaP and PC-3 cells were significantly elevated in a dose dependent manner after exposure to curcumin. In addition, curcumin induces the G2/M cell cycle arrest of LNCaP and PC-3 cells in a dose dependent manner. Mechanistically, we found that curcumin upregulated the protein level of NF- κ B inhibitor I κ B α and downregulated protein levels of c-Jun and

AR. These data suggest that curcumin is a promising agent for the treatment of both androgen-dependent and androgen-independent prostate cancer.

[328]

TÍTULO / TITLE: - XIAP and P-glycoprotein co-expression is related to imatinib resistance in chronic myeloid leukemia cells.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Jul 25. pii: S0145-2126(13)00200-2. doi: 10.1016/j.leukres.2013.06.014.

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

[1016/j.leukres.2013.06.014](#)

AUTORES / AUTHORS: - Silva KL; de Souza PS; Nestal de Moraes G; Moellmann-Coelho A; Vasconcelos FD; Maia RC

INSTITUCIÓN / INSTITUTION: - Laboratorio de Hemato-Oncología Celular e Molecular, Programa de Hemato-Oncología Molecular, Coordenacao Geral Tecnico-Cientifica (CGCT), Instituto Nacional de Cancer (INCA) and Programa de Pos-Graduacao em Oncologia/INCA, Brazil.

RESUMEN / SUMMARY: - P-glycoprotein (Pgp) and XIAP co-expression has been discussed in the process of the acquisition of multidrug resistance (MDR) in cancer. Here, we evaluated XIAP and Pgp expression in chronic myeloid leukemia (CML) samples, showing a positive correlation between them. Furthermore, we evaluated the effects of imatinib in XIAP and Pgp expression using CML cell lines K562 (Pgp-) and K562-Lucena (Pgp+). Imatinib increased XIAP and Pgp expression in K562-Lucena cells, while in K562 cells a downregulation of these proteins was observed, suggesting that imatinib induces an increment of MDR phenotype of CML cells that previously exhibit high levels of Pgp/XIAP co-expression.

[329]

TÍTULO / TITLE: - Toll-like receptors 3, 4 and 9 in hepatocellular carcinoma: Relationship with clinicopathological characteristics and prognosis.

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

REVISTA / JOURNAL: - Hepatol Res. 2013 Jun 6. doi: 10.1111/hepr.12180.

●● Enlace al texto completo (gratis o de pago) [1111/hepr.12180](#)

AUTORES / AUTHORS: - Eiro N; Altadill A; Juarez LM; Rodriguez M; Gonzalez LO; Atienza S; Bermudez S; Fernandez-Garcia B; Fresno-Forcelledo MF; Rodrigo L; Vizoso FJ

INSTITUCIÓN / INSTITUTION: - Research Unit, Foundation Hospital of Jove, Gijon, España.

RESUMEN / SUMMARY: - AIM: Hepatocellular carcinoma (HCC) is in the 10 leading cancer types, being difficult to detect as most of patients who develop this tumor have no symptoms other than those related to their long-standing

liver disease. The liver is constantly exposed to bacterial products, viral infection, alcohol or other products, which may be the cause of chronic liver damage, and thus an increasing risk for HCC. Toll-like receptors (TLR) have gained an extraordinary interest in cancer research due to their role in several biological processes such as innate immune responses, the induction of adaptive immune responses, regulation of inflammation, wound healing and carcinogenesis. Therefore, the aim of this study was to investigate the expression and clinical relevance of TLR3, 4 and 9 in HCC. METHODS: The expression levels of TLR3, TLR4 and TLR9 were analyzed in tumors from 30 patients with HCC. The analysis was performed by immunohistochemistry. Results were correlated with various clinicopathological findings and with overall survival. RESULTS: TLR3 was significantly high in large tumors (>4 cm in diameter) compared with small tumors ($P < 0.05$). Our results demonstrated that patients whose tumors showed both TLR4 and TLR9 positive immunostaining had poor prognosis. In addition, TLR9 expression by fibroblast-like cells was significantly associated with a shortened overall survival ($P = 0.015$). CONCLUSION: The results demonstrated an association between TLR3, TLR4 and TLR9 expression and tumor aggressiveness and poor prognosis in HCC.

[330]

TÍTULO / TITLE: - STAT pathway in the regulation of zoledronic acid-induced apoptosis in chronic myeloid leukemia cells.

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

REVISTA / JOURNAL: - Biomed Pharmacother. 2013 Jul;67(6):527-32. doi: 10.1016/j.biopha.2013.04.006. Epub 2013 May 7.

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

1016/j.biopha.2013.04.006

AUTORES / AUTHORS: - Kiper HD; Tezcanli Kaymaz B; Gokbulut AA; Selvi N; Avci CB; Kosova B; Iskender G; Yandim MK; Gunduz C; Sahin F; Baran Y; Saydam G

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, School of Medicine, Ege University, Bornova, Izmir, Turkey.

RESUMEN / SUMMARY: - In this study, we aimed to evaluate the cytotoxic and apoptotic effects of zoledronic acid on K562 chronic myeloid leukemia (CML) cells and to examine the roles of STAT genes on zoledronic acid-induced apoptosis. The results showed that zoledronic acid decreased proliferation, and induced apoptosis in K562 cells in a dose- and time-dependent manner. mRNA and protein levels of STAT3, -5^a and -5B genes were significantly reduced in zoledronic acid-treated K562 cells. These data indicated that STAT inhibition by zoledronic acid may be therapeutic in CML patients following the confirmation with clinical studies.

[331]

TÍTULO / TITLE: - Cisplatin-induced non-apoptotic death of pancreatic cancer cells requires mitochondrial cyclophilin-D-p53 signaling.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 8. pii: S0006-291X(13)01113-3. doi: 10.1016/j.bbrc.2013.06.103.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.06.103

AUTORES / AUTHORS: - Chen B; Xu M; Zhang H; Wang JX; Zheng P; Gong L; Wu GJ; Dai T

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, East Hospital Affiliated to Tongji University in Shanghai, Shanghai, China.

RESUMEN / SUMMARY: - The pancreatic cancer remains a fatal disease for the majority of patients. Cisplatin has displayed significant cytotoxic effects against the pancreatic cancer cells, however the underlying mechanisms remain inconclusive. Here, we found that cisplatin mainly induced non-apoptotic death of the pancreatic cancer cells (AsPC-1 and Capan-2), which was associated with a significant p53 activation (phosphorylation and accumulation). Further, activated p53 was found to translocate to mitochondria where it formed a complex with cyclophilin D (Cyp-D). We provided evidences to support that mitochondrial Cyp-D/p53 complexation might be critical for cisplatin-induced non-apoptotic death of pancreatic cancer cells. Inhibition of Cyp-D by its inhibitor cyclosporine A (CsA), or by shRNA-mediated knockdown suppressed cisplatin-induced pancreatic cancer cell death. Both CsA and Cyp-D knockdown also disrupted the Cyp-D/p53 complex formation in mitochondria. Meanwhile, the pancreatic cancer cells with p53 knockdown were resistant to cisplatin. On the other hand, HEK-293 over-expressing Cyp-D were hyper-sensitive to cisplatin. Interestingly, camptothecin (CMT)-induced pancreatic cancer cell apoptotic death was not affected CsA or Cyp-D knockdown. Together, these data suggested that cisplatin-induced non-apoptotic death requires mitochondria Cyp-D-p53 signaling in pancreatic cancer cells.

[332]

TÍTULO / TITLE: - Knockdown of Inhibitor of Growth Protein 2 Inhibits Cell Invasion and Enhances Chemosensitivity to 5-FU in Human Gastric Cancer Cells.

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

REVISTA / JOURNAL: - Dig Dis Sci. 2013 Jul 18.

●● Enlace al texto completo (gratis o de pago) [1007/s10620-013-2796-](http://1007/s10620-013-2796-5)

[5](#)

AUTORES / AUTHORS: - Zhong J; Yang L; Liu N; Zheng J; Lin CY

INSTITUCIÓN / INSTITUTION: - Department of Oncology, The Fifth Hospital of Wuhan, No 122 Xianzheng Street, Hanyang District, Wuhan, 430050, Hubei, People's Republic of China, zjdays@163.com.

RESUMEN / SUMMARY: - BACKGROUND: The inhibitor of growth (ING) family is involved in multiple cellular functions, but the role of ING2 in gastric cancer progression is unclear. AIM: To investigate the effects of ING2 gene knockdown on chemosensitivity to 5-fluorouracil (5-FU) in human gastric cancer cells and its possible mechanisms. METHODS: Short hairpin RNA (shRNA) targeting ING2 (shING2) was transfected into MGC-803 cells using Lipofectamine 2000, and stable transfection cell lines were established using G418. Cell viability, cell cycle distribution, cell apoptosis, and invasive ability were measured to determine the influence of ING2 knockdown on cell biologic characteristics. Messenger RNA (mRNA) and protein levels of ING2, cyclin D1, NF-kappaB/p65, and several matrix metalloproteinases (MMPs) were determined by use of real-time polymerase chain reaction (PCR) or Western blotting, respectively. RESULTS: Our results showed that ING2 knockdown induced cell apoptosis and inhibited cell viability significantly ($P < 0.05$). Additionally, ING2 knockdown induced a specific G0/G1 arrest. Furthermore, the suppression of ING2 could enhance the chemosensitivity of gastric cancer cells to 5-FU significantly. Moreover, knockdown of ING2 expression significantly reduced cellular metastatic ability and expression of MMPs in MGC-803 cells. The expression of cyclin D1 and NF-kappaB/p65 was also markedly inhibited in MGC-803/shING2 cells compared with control cells. CONCLUSIONS: ING2 not only plays an essential role in the growth and invasion of MGC-803 cells but also represents a potential approach to chemosensitization therapy in human gastric cancer.

[333]

TÍTULO / TITLE: - Cytotoxic constituents from *Celastrus paniculatus* induce apoptosis and autophagy in breast cancer cells.

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

REVISTA / JOURNAL: - *Phytochemistry*. 2013 Jun 27. pii: S0031-9422(13)00204-5. doi: 10.1016/j.phytochem.2013.05.022.

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

[1016/j.phytochem.2013.05.022](#)

AUTORES / AUTHORS: - Weng JR; Yen MH; Lin WY

INSTITUCIÓN / INSTITUTION: - Department of Biological Science and Technology, China Medical University, Taichung 404, Taiwan. Electronic address: columnster@gmail.com.

RESUMEN / SUMMARY: - *Celastrus paniculatus* is a traditional medicinal plant with diverse pharmacological activities. To identify its bioactive constituents, three new beta-dihydroagarofuranoid sesquiterpenes were isolated from the whole plant, of which the major constituent is (1alpha,2alpha,8beta,9beta)-1,8-bis(acetyloxy)-2,9-bis(benzoyloxy)-14-hydroxy-beta-dihydroagarofuran. It was assessed for its antiproliferative activity, and it suppressed the viability of MCF-7 breast cancer cells with an IC50 of 17+/-1muM. This growth inhibition was, in

part, attributable to apoptosis. Moreover, this drug treatment led to LC3B-II accumulation, indicative of autophagy. Western blot analysis established its ability to target a broad range of signaling effectors related to survival and cell cycle progression, including Akt, NF-kappaB, p53, and MAP kinases. In addition, flow cytometry analysis indicates increased reactive oxygen species production in response to this compound. Taken together, these findings suggest a pleiotropic mode of mechanism that underlies the antiproliferative activity of this compound in MCF-7 breast cancer cells.

[334]

TÍTULO / TITLE: - Mimic of Manganese superoxide dismutase induces apoptosis in human acute myelocytic leukemia cells.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 24.

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

[3109/10428194.2013.825904](#)

AUTORES / AUTHORS: - Wang YH; Xu XJ; Zhang LF; Li HL

RESUMEN / SUMMARY: - Abstract Increasing Manganese superoxide dismutase (MnSOD) expression could suppress the malignant phenotype in various cancer cell lines and suppress tumor formation in xenograft and transgenic mouse models. Mimic of Manganese superoxide dismutase (MnSODm), synthesized by chemical method, has been shown to possess anti-tumor. However, the anti-cancer activity of MnSODm in acute myeloid leukemia (AML) is still obscure. In this study, we investigated the effects of MnSODm on the apoptosis of human leukemia HL-60 cells. The result showed MnSODm significantly reduced the proliferation of HL-60 cells in a concentration and a time-dependent manner. By flow cytometric analysis, we found that MnSODm treatment resulted in an increased apoptosis in HL-60 cells. Further analysis demonstrated the involvement of activation of caspase cascade, cleavage of poly (ADP-ribose) polymerase (PARP), and release of cytochrome c in MnSODm-induced apoptosis. The results also showed that the expression of anti-apoptotic Bcl-2 and Bid were dose-dependently decreased, whereas the expressions of pro-apoptotic Bax protein were increased. Thus, MnSODm-induced apoptosis in HL-60 cells via mitochondria-mediated, caspases-dependent pathways. MnSODm inhibition of Akt phosphorylation may contribute to MnSODm-mediated acute myeloid leukemia cell growth inhibition and apoptosis induction.

[335]

TÍTULO / TITLE: - Neem leaf extract induces cell death by apoptosis and autophagy in B-chronic lymphocytic leukemia cells.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 1.

- Enlace al texto completo (gratis o de pago)

[3109/10428194.2013.807927](https://doi.org/10.1016/j.abb.2013.07.016)

AUTORES / AUTHORS: - Chitta KS; Khan AN; Ersing N; Swaika A; Masood A; Paulus A; Qadeer A; Advani P; Sher T; Miller KC; Lee K; Chanan-Khan AA

INSTITUCIÓN / INSTITUTION: - Department of Cancer Biology.

RESUMEN / SUMMARY: - Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and is currently incurable. To expand the therapeutic armamentarium, we investigated neem leaf extract (NLE) after a patient with CLL demonstrated disease regression upon taking oral NLE. NLE-mediated apoptosis was examined in peripheral blood mononuclear cells (PBMCs) from 41 patients with CLL. NLE induced a dose-dependent reduction in CLL cell viability with significant apoptosis observed at 0.06% (w/v) by 24 h. Annexin-V staining and poly(ADP-ribose) polymerase 1 (PARP-1) and caspase 3 cleavage were observed after NLE treatment. However, a pan-caspase inhibitor only partially blocked NLE-mediated cell death. NLE also caused loss of mitochondrial outer membrane permeability and nuclear translocation of apoptosis-inducing factor. Furthermore, NLE treatment resulted in LC3-I cleavage. Biochemical analyses revealed that NLE also inhibits Bcl-2 and p53 proteins. In summary, NLE exhibits anti-leukemic properties in patient primary CLL cells and demonstrates clinical efficacy, warranting further investigation as a potential therapy for CLL.

[336]

TÍTULO / TITLE: - Reactive oxygen species mediate tolfenamic acid-induced apoptosis in human colorectal cancer cells.

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

REVISTA / JOURNAL: - Arch Biochem Biophys. 2013 Jul 26. pii: S0003-9861(13)00223-3. doi: 10.1016/j.abb.2013.07.016.

- Enlace al texto completo (gratis o de pago) [1016/j.abb.2013.07.016](https://doi.org/10.1016/j.abb.2013.07.016)

AUTORES / AUTHORS: - Jeong JB; Choi J; Baek SJ; Lee SH

INSTITUCIÓN / INSTITUTION: - Department of Nutrition and Food Science, College of Agriculture and Natural Resources, University of Maryland, College Park, MD 20742, USA.

RESUMEN / SUMMARY: - Several studies have shown substantial evidences that non-steroidal anti-inflammatory drugs (NSAIDs) exert anticancer effects by generating reactive oxygen species (ROS). Tolfenamic acid (TA) is one of the traditional NSAIDs widely used for treatment of migraine. TA has anti-cancer activities in several human cancer models. In this study, we report that generation of ROS by TA leads to apoptosis through modulation of several pathways in human colorectal cancer cells. TA induced rapid generation of intracellular ROS and led to an increase of phosphorylation of H2AX, a tail moment of comet and distribution of fragmented genomic DNA traces. Treatment of N-acetyl-L-cysteine (NAC) abolished TA-induced phosphorylation

of H2AX and apoptosis. Treatment of TA resulted in an increase of nuclear factor-kappaB (NF-kappaB) transcriptional activity through inhibitor of kappa B (IkappaB-alpha) degradation and subsequent p65 nuclear translocation. In addition, TA increased apoptosis-inducing activating transcription factor 3 (ATF3) expression. However, the treatment of NAC abolished TA-mediated NF-kappaB activation and ATF3 expression and chemical inhibition of NF-kappaB or knockdown of p65 significantly attenuated TA-induced ATF3 expression. Our finding indicates that ROS-mediated DNA damage and subsequent activation of NF-kappaB and ATF3 expression plays a significant role in TA-induced apoptosis in human colorectal cancer cells.

[337]

TÍTULO / TITLE: - Generalized lymphadenopathy mimicking malignant lymph node metastases after interferon-alpha2b therapy for melanoma.

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

REVISTA / JOURNAL: - Melanoma Res. 2013 Aug;23(4):336-9. doi: 10.1097/CMR.0b013e3283632ca7.

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

[1097/CMR.0b013e3283632ca7](#)

AUTORES / AUTHORS: - Yune S; Jang KT; Jung SM; Kim JH; Lee J

INSTITUCIÓN / INSTITUTION: - Departments of aMedicine bPathology cSurgery dHematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - A patient, who complained of axillary swelling, was diagnosed with malignant melanoma of stage IIb and received adjuvant high-dose interferon-alpha2b (HDI) therapy for 3 months. Computed tomography demonstrated multiple, generalized lymph node enlargement with high fluorine-18-fluorodeoxyglucose uptake (6.6 of the standardized uptake value) on PET. Histological examination of the axillary lymph node revealed reactive hyperplasia, without evidence of malignant cells. Discontinuation of interferon therapy for 6 weeks resulted in near-complete resolution of the lymphadenopathies. HDI therapy was therefore resumed at a reduced dose and was continued for 25 weeks without recurrence of the lymphadenopathies. HDI therapy is the only adjuvant therapy proven to be effective in malignant melanoma. The release of various additional cytokines is stimulated by interferon, which is responsible for the more common side effects of this therapy. The cytokines are also likely to stimulate helper T cells and induce T-cell sequestration within lymph nodes. These actions are possibly associated with generalized lymph node enlargement in some patients undergoing HDI therapy. The results from the present case indicate that HDI therapy can be safely maintained after confirming the benign nature of the lymphadenopathies that occur during the treatment.

[338]

TÍTULO / TITLE: - MR elastography derived shear stiffness-a new imaging biomarker for the assessment of early tumor response to chemotherapy.

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

REVISTA / JOURNAL: - Magn Reson Med. 2013 Jun 25. doi: 10.1002/mrm.24825.

●● Enlace al texto completo (gratis o de pago) [1002/mrm.24825](#)

AUTORES / AUTHORS: - Pepin KM; Chen J; Glaser KJ; Mariappan YK; Reuland B; Ziesmer S; Carter R; Ansell SM; Ehman RL; McGee KP

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Engineering, Mayo Graduate School, Rochester, Minnesota, USA.

RESUMEN / SUMMARY: - Purpose: The overall goal is to develop magnetic resonance elastography derived shear stiffness as a biomarker for the early identification of chemotherapy response, allowing dose, agent type and treatment regimen to be tailored on a per patient basis, improving therapeutic outcome and minimizing normal tissue toxicity. The specific purpose of this study is to test the feasibility of this novel biomarker to measure the treatment response in a well-known chemotherapy model. Methods: Tumors were grown in the right flank of genetically modified mice by subcutaneous injection of DoHH2 (non-Hodgkin's lymphoma) cells. Magnetic resonance elastography was used to quantify tumor stiffness before and after injection of a chemotherapeutic agent or saline. Histological tests were also performed on the tumors. Results: A significant decrease ($P < 0.0001$) in magnetic resonance elastography-derived tumor shear stiffness was observed within 4 days of chemotherapy treatment, while no appreciable change was observed in saline-treated tumors. No significant change in volume occurred at this early stage, but there were decreased levels of cellular proliferation in chemotherapy-treated tumors. Conclusion: These results demonstrate that magnetic resonance elastography-derived estimates of shear stiffness reflect an initial response to cytotoxic therapy and suggest that this metric could be an early and sensitive biomarker of tumor response to chemotherapy. Magn Reson Med, 2013. © 2013 Wiley Periodicals, Inc.

[339]

TÍTULO / TITLE: - 5-aminolaevulinic acid/photo-dynamic therapy and gefitinib in non-small cell lung cancer cell lines: a potential strategy to improve gefitinib therapeutic efficacy.

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

REVISTA / JOURNAL: - Cell Prolif. 2013 Aug;46(4):382-95. doi: 10.1111/cpr.12040.

●● Enlace al texto completo (gratis o de pago) [1111/cpr.12040](#)

AUTORES / AUTHORS: - Postiglione I; Chiaviello A; Aloj SM; Palumbo G

INSTITUCIÓN / INSTITUTION: - Department of Molecular Medicine and Health Biotechnology, University Federico II, Naples, 80131, Italy.

RESUMEN / SUMMARY: - **OBJECTIVES:** Often, non-small cell lung cancers (NSCLC) respond only poorly to the tyrosine kinase inhibitor (TKI) gefitinib, which targets the epidermal growth factor receptor (EGFR), these poor responders EGFRs lacking activating mutations. In this study, we have attempted to improve TKI response of NSCLC cell lines (A549 and H1299) devoid of EGFR mutations, by combination of gefitinib and 5-ALA/photodynamic therapy (PDT). **MATERIALS AND METHODS:** Cells of the two lines were incubated with gefitinib (from 0.5 to 50 nm, for 48 h) then irradiated at doses ranging from 4 to 20 J/cm²; 5-ALA concentration and incubation time were kept constant (1 mM for 3 h). We analysed cell viability, colony-forming efficiency, cell cycle parameters, proteasome and NF-kappaB activity and expression patterns of specific proteins, after individual or combined treatments. **RESULTS:** Effects (antagonistic, additive or synergistic) of combination treatment were evaluated using a predictive model (combination index) for expected interactive effects and results are consistent with mutual potentiation exceeding simple additivity. Investigation of molecular mechanisms underlying cytotoxic effects indicated that combination treatment impaired proteasome function, inhibited NF-kappaB transcriptional activity and hampered AKT pro-survival signalling. **CONCLUSIONS:** The results of this study show that poor response of cells devoid of EGFR activating mutations to TKIs, can be overcome by combining gefitinib with 5-ALA/photodynamic therapy (PDT).

[340]

TÍTULO / TITLE: - The apoptosis pathway of photodynamic therapy using 9-HpbD-a in AMC-HN3 human head and neck cancer cell line and in vivo.

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

REVISTA / JOURNAL: - Gen Physiol Biophys. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [4149/gpb_2013040](#)

AUTORES / AUTHORS: - Ahn JC

INSTITUCIÓN / INSTITUTION: - Medical Laser Research Center, Dankook University, 29-1, Anseo-dong, Cheonan, Chungnam, Korea.

jcahn@dankook.ac.kr.

RESUMEN / SUMMARY: - 9-Hydroxyphorbide-a (9-HpbD-a), a new photosensitizer was extracted from the green alga *Spirulina platensis*. The anticancer effects of photodynamic therapy (PDT) treatment using 9-HpbD-a against human head and neck cancer cell HN3 and in vivo mice model were investigated. Cells were incubated with 9-HpbD-a for at least 6 hours or more followed by the laser irradiation. Cytotoxicity of 9-HpbD-a against HN3 cell was determined using the MTT assay, propidium iodide and Hoechst 33342 staining and transmission electron microscopy (TEM). To determine the mechanism of cell death, Western blot analysis was performed. The antitumor effect was

confirmed in a cancer cell xenograft nude mouse model by photodynamic therapy (PDT) using 9-HpbD-a. For normal control and the 9-HpbD-a only treated group, tumor tissues showed continuous tumor growth (100%). For laser only treated experimental group, 3 treatments showed no remission (75.0%), and was one recurrence (25.0%). Out of 16 tumors in the fourth group of photodynamic treatment, 10 cured (62.5%), 4 recurrence (25.0%), and 2 did not heal (12.5%) were confirmed. PDT using a 9-HpbD-a and 665 nm diode laser showed significant antitumor effects. Thus PDT using 9-HpbD-a can be a useful new treatment method in the treatment of cancer in the future.

[341]

TÍTULO / TITLE: - Targeting tumour energy metabolism potentiates the cytotoxicity of 5-aminolevulinic acid photodynamic therapy.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 16. doi: 10.1038/bjc.2013.391.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.391](#)

AUTORES / AUTHORS: - Golding JP; Wardhaugh T; Patrick L; Turner M; Phillips JB; Bruce JI; Kimani SG

INSTITUCIÓN / INSTITUTION: - Department of Life, Health & Chemical Sciences, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK.

RESUMEN / SUMMARY: - Background:Cancerous cells usually exhibit increased aerobic glycolysis, compared with normal tissue (the Warburg effect), making this pathway an attractive therapeutic target.Methods:Cell viability, cell number, clonogenic assay, reactive oxygen (ROS), ATP, and apoptosis were assayed in MCF-7 tumour cells and corresponding primary human mammary epithelial cells (HMEC).Results:Combining the glycolysis inhibitors 2-deoxyglucose (2DG; 180 mM) or lonidamine (300 µM) with 10 J cm⁻² 5-aminolevulinic acid (ALA) photodynamic therapy (PDT) increases MCF-7 cytotoxicity (by 3.5-fold to 70% death after 24 h, and by 10-fold in 9-day clonogenic assays). However, glycolysis inhibition only slightly increases HMEC PDT cytotoxicity (between two-fold and three-fold to a maximum of 9% death after 24 h). The potentiation of PDT cytotoxicity only occurred if the glycolysis inhibitors were added after ALA incubation, as they inhibited intracellular accumulation of photosensitiser if coincubated with ALA.Conclusion:As 2DG and lonidamine are already used as cancer chemotherapeutic agents, our results are directly translatable to combination therapies with existing topical PDT.British Journal of Cancer advance online publication 16 July 2013; doi:10.1038/bjc.2013.391
www.bjcancer.com.

[342]

TÍTULO / TITLE: - The oestrogen receptor coactivator CARM1 has an oncogenic effect and is associated with poor prognosis in breast cancer.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jul;140(2):307-16. doi: 10.1007/s10549-013-2614-y. Epub 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1007/s10549-013-2614-](#)

[y](#)

AUTORES / AUTHORS: - Habashy HO; Rakha EA; Ellis IO; Powe DG

INSTITUCIÓN / INSTITUTION: - Department of Histopathology, Nottingham City Hospital, School of Molecular Medical Sciences, The University of Nottingham and Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, NG5 1PB, UK.

RESUMEN / SUMMARY: - The coactivator-associated arginine methyltransferase-1 (CARM1) is implicated in regulation of oestrogen receptor (ER) alpha-mediated gene pathways in response to ER activation. It plays an important role in breast cancer growth by regulating the E2F1 expression suggesting that CARM1 could be a target in the subclassification of oestrogen-dependent breast cancer. This study aims to investigate the clinical and biological importance of CARM1 protein expression in a large (1,130 patients), well-characterised and annotated series of invasive breast cancers using tissue microarrays and immunohistochemistry. In the whole series, increased CARM1 expression is correlated with features associated with aggressive behaviour such as young age, premenopausal status, large tumour size and high tumour grade. There is a positive correlation between CARM1 expression and biomarkers associated with non-luminal phenotype and poor prognosis such as HER2, basal cytokeratins, EGFR, p53 and the proliferation markers Ki67, TK1, CD71 and Cyclin E. Negative associations with the luminal-associated markers including steroid receptors and luminal cytokeratins are found. Similar associations are identified in the ER-positive/luminal subgroup (n = 767). Outcome analyses indicate that CARM1 expression is an independent predictor of shorter breast cancer-specific survival and disease-free interval in the whole series and in the ER-positive subgroup. CARM1 shows an oncogenic effect in breast cancer and its expression is associated with poor prognosis. CARM1 could be a potential marker of luminal class subclassification and for target therapy, particularly in the ER-positive luminal-like subgroup.

[343]

TÍTULO / TITLE: - Toxicogenomic outcomes predictive of forestomach carcinogenesis following exposure to benzo(a)pyrene: Relevance to human cancer risk.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Jun 2. pii: S0041-008X(13)00257-3. doi: 10.1016/j.taap.2013.05.027.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.05.027](#)

AUTORES / AUTHORS: - Labib S; Guo CH; Williams A; Yauk CL; White PA; Halappanavar S

INSTITUCIÓN / INSTITUTION: - Environmental and Radiation Health Sciences Directorate, Health Canada, Ottawa, Ontario K1A 0K9, Canada. Electronic address: Sarah.Labib@hc-sc.gc.ca.

RESUMEN / SUMMARY: - Forestomach tumors are observed in mice exposed to environmental carcinogens. However, the relevance of this data to humans is controversial because humans lack a forestomach. We hypothesize that an understanding of early molecular changes after exposure to a carcinogen in the forestomach will provide mode-of-action information to evaluate the applicability of forestomach cancers to human cancer risk assessment. In the present study we exposed mice to benzo(a)pyrene (BaP), an environmental carcinogen commonly associated with tumors of the rodent forestomach. Toxicogenomic tools were used to profile gene expression response in the forestomach. Adult MutaMouse males were orally exposed to 25, 50, and 75mgBaP/kg-body-weight/day for 28 consecutive days. The forestomach was collected three days post-exposure. DNA microarrays, real-time RT-qPCR arrays, and protein analyses were employed to characterize responses in the forestomach. Microarray results showed altered expression of 414 genes across all treatment groups (+/-1.5 fold; false discovery rate adjusted $P \leq 0.05$). Significant downregulation of genes associated with phase II xenobiotic metabolism and increased expression of genes implicated in antigen processing and presentation, immune response, chemotaxis, and keratinocyte differentiation were observed in treated groups in a dose-dependent manner. A systematic comparison of the differentially expressed genes in the forestomach from the present study to differentially expressed genes identified in human diseases including human gastrointestinal tract cancers using the NextBio Human Disease Atlas showed significant commonalities between the two models. Our results provide molecular evidence supporting the use of the mouse forestomach model to evaluate chemically-induced gastrointestinal carcinogenesis in humans.

[344]

TÍTULO / TITLE: - Anticancer effects of sweet potato protein on human colorectal cancer cells.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Jun 7;19(21):3300-8. doi: 10.3748/wjg.v19.i21.3300.

●● Enlace al texto completo (gratis o de pago) 3748/wjg.v19.i21.3300

AUTORES / AUTHORS: - Li PG; Mu TH; Deng L

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Agro-products Processing, Ministry of Agriculture, Institute of Agro-products Processing Science and

Technology, Chinese Academy of Agricultural Sciences, Beijing 100193, China.

RESUMEN / SUMMARY: - AIM: To investigate the effects of proteins purified from sweet potato storage roots on human colorectal cancer cell lines. METHODS: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, Hoechst 33258 nuclear staining and Boyden transwell chamber methods were used to determine whether purified sweet potato protein (SPP) from fresh sweet potato roots affected proliferation, migration and invasion, respectively, of human colorectal cancer SW480 cells in vitro. The inhibitory effects of SPP on growth of human colorectal cancer HCT-8 cells intraperitoneally xenografted in nude mice and spontaneous lung metastasis of murine Lewis lung carcinoma 3LL cells subcutaneously transplanted in C57 BL/6 mice were also investigated in vivo. RESULTS: SPP inhibited the proliferation of SW480 cells in a dose-dependent manner, with an IC₅₀ value of 38.732 μmol/L ($r(2) = 0.980$, $P = 0.003$) in the MTT assay. Hoechst 33258 nuclear staining further revealed inhibition of cell viability and induction of apoptosis by SPP. The transwell assay disclosed significant reduction in migrated cells/field by 8 μmol/L SPP (8.4 ± 2.6 vs 23.3 ± 5.4, $P = 0.031$) and invaded cells/field through the ECMatrix by 0.8 μmol/L SPP, compared with the control (25.2 ± 5.2 vs 34.8 ± 6.1, $P = 0.038$). Both intraperitoneal (ip) and intragastric (ig) administration of SPP led to significant suppression of growth of intraperitoneally inoculated HCT-8 cells in nude mice to 58.0% ± 5.9% ($P = 0.037$) and 43.5% ± 7.1% ($P = 0.004$) of the controls, respectively, after 9 d treatment. Bloody ascites additionally disappeared after ip injection of trypsin inhibitor. Notably, ig and ip administration of SPP induced a significant decrease in spontaneous pulmonary metastatic nodule formation in C57 BL/6 mice (21.0 ± 12.3 and 27.3 ± 12.7 nodules/lung vs 42.5 ± 4.5 nodules/lung in controls, respectively, $P < 0.05$) after 25 d treatment. Moreover, the average weight of primary tumor nodules in the hind leg of mice decreased from 8.2 ± 1.3 g/mice in the control to 6.1 ± 1.4 g/mice in the ip group ($P = 0.035$). CONCLUSION: SPP exerts significant antiproliferative and antimetastatic effects on human colorectal cancer cell lines, both in vitro and in vivo.

[345]

TÍTULO / TITLE: - Trichodermin induces cell apoptosis through mitochondrial dysfunction and endoplasmic reticulum stress in human chondrosarcoma cells.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Jun 24. pii: S0041-008X(13)00283-4. doi: 10.1016/j.taap.2013.06.010.

●● Enlace al texto completo (gratis o de pago) 1016/j.taap.2013.06.010

AUTORES / AUTHORS: - Su CM; Wang SW; Lee TH; Tzeng WP; Hsiao CJ; Liu SC; Tang CH

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Basic Medical Science, China Medical University, Taichung, Taiwan.

RESUMEN / SUMMARY: - Chondrosarcoma is the second most common primary bone tumor, and it responds poorly to both chemotherapy and radiation treatment. Nalanthamala psidii was described originally as Myxosporium in 1926. This is the first study to investigate the anti-tumor activity of trichodermin (trichothec-9-en-4-ol, 12,13-epoxy-, acetate), an endophytic fungal metabolite from N. psidii against human chondrosarcoma cells. We demonstrated that trichodermin induced cell apoptosis in human chondrosarcoma cell lines (JJ012 and SW1353 cells) instead of primary chondrocytes. In addition, trichodermin triggered endoplasmic reticulum (ER) stress protein levels of IRE1, p-PERK, GRP78, and GRP94, which were characterized by changes in cytosolic calcium levels. Furthermore, trichodermin induced the upregulation of Bax and Bid, the downregulation of Bcl-2, and the dysfunction of mitochondria, which released cytochrome c and activated caspase-3 in human chondrosarcoma. In addition, animal experiments illustrated reduced tumor volume, which led to an increased number of terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL)-positive cells and an increased level of cleaved PARP protein following trichodermin treatment. Together, this study demonstrates that trichodermin is a novel anti-tumor agent against human chondrosarcoma cells both in vitro and in vivo via mitochondrial dysfunction and ER stress.

[346]

TÍTULO / TITLE: - Pharmacodynamic modeling of cell cycle and apoptotic effects of gemcitabine on pancreatic adenocarcinoma cells.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2226-](#)

[6](#)

AUTORES / AUTHORS: - Hamed SS; Straubinger RM; Jusko WJ

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, 404 Kapoor Hall, Buffalo, NY, 14214, USA.

RESUMEN / SUMMARY: - **PURPOSE:** The standard of care for treating patients with pancreatic adenocarcinomas includes gemcitabine (2',2'-difluorodeoxycytidine). Gemcitabine primarily elicits its response by stalling the DNA replication forks of cells in the S phase of the cell cycle. To provide a quantitative framework for characterizing the cell cycle and apoptotic effects of gemcitabine, we developed a pharmacodynamic model in which the activation of cell cycle checkpoints or cell death is dependent on gemcitabine exposure. **METHODS:** Three pancreatic adenocarcinoma cell lines (AsPC-1, BxPC-3, and MiaPaca-2) were exposed to varying concentrations (0-100,000 ng/mL) of gemcitabine over a period of 96 h in order to quantify proliferation kinetics and

cell distributions among the cell cycle phases. The model assumes that the drug can inhibit cycle-phase transitioning in each of the 3 phases (G1, S, and G2/M) and can cause apoptosis of cells in G1 and G2/M phases. Fitting was performed using the ADAPT5 program. RESULTS: The time course of gemcitabine effects was well described by the model, and parameters were estimated with good precision. Model predictions and experimental data show that gemcitabine induces cell cycle arrest in the S phase at low concentrations, whereas higher concentrations induce arrest in all cell cycle phases. Furthermore, apoptotic effects of gemcitabine appear to be minimal and take place at later time points. CONCLUSION: The pharmacodynamic model developed provides a quantitative, mechanistic interpretation of gemcitabine efficacy in 3 pancreatic cancer cell lines, and provides useful insights for rational selection of chemotherapeutic agents for combination therapy.

[347]

TÍTULO / TITLE: - A Multicenter Phase 1 Study of EMD 525797 (DI17E6), a Novel Humanized Monoclonal Antibody Targeting α v Integrins, in Progressive Castration-resistant Prostate Cancer with Bone Metastases After Chemotherapy.

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

REVISTA / JOURNAL: - Eur Urol. 2013 Jun 6. pii: S0302-2838(13)00565-4. doi: 10.1016/j.eururo.2013.05.051.

- Enlace al texto completo (gratis o de pago)

1016/j.eururo.2013.05.051

AUTORES / AUTHORS: - Wirth M; Heidenreich A; Gschwend JE; Gil T; Zastrow S; Laniado M; Gerloff J; Zuhlsdorf M; Mordenti G; Uhl W; Lannert H

INSTITUCIÓN / INSTITUTION: - Department of Urology, University Hospital Carl Gustav Carus Dresden, Dresden, Germany. Electronic address:

Manfred.Wirth@uniklinikum-dresden.de.

RESUMEN / SUMMARY: - BACKGROUND: EMD 525797 (DI17E6) is a deimmunized, humanized monoclonal immunoglobulin G2 antibody against the α v subunit of human integrins. Blocking α v integrins may be an effective strategy for inhibiting prostate cancer (PCa) metastasis. OBJECTIVE: Evaluate EMD 525797 safety/tolerability and pharmacokinetics (PK) in castration-resistant PCa patients. Secondary objectives included antitumor activity assessments. DESIGN, SETTING, AND PARTICIPANTS: A phase 1 open-label study in 26 patients (four European centers). Eligible patients (≥ 18 yr) had histologically proven PCa with bone metastases after prior chemotherapy and evidence of progressive disease (PD) based on prostate-specific antigen (PSA) values. INTERVENTION: Patients received three intravenous EMD 525797 infusions (250, 500, 1000, or 1500mg every 2 wk). OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Treatment-emergent adverse events (TEAEs) and dose-limiting toxicities (DLTs) were

assessed. PK parameters were calculated according to noncompartmental standard methods. Antitumor activity measures were response after 6 wk, changes in PSA levels, and pain interference total score. Descriptive statistics were used. RESULTS AND LIMITATIONS: Patients were treated for a mean of 16.8 +/- 16.7 wk. No DLTs were reported in any of the cohorts. All patients experienced TEAEs, which were considered drug-related in 11 patients. Four deaths occurred during the trial and were considered not related to EMD 525797. EMD 525797 showed dose-dependent, nonlinear PK. Eighteen of 26 patients did not show PD for >=18 wk. Two patients (500-mg cohort), treated for 42.4 and 76.3 wk, had clinically significant PSA reductions and pain relief, including one patient with confirmed partial response. This trial was not specifically designed to assess clinical activity, and further investigations are needed in randomized controlled trials. CONCLUSIONS: No DLTs were reported in any of the evaluated cohorts. There was evidence of clinical activity. For the currently ongoing phase 2 trial, EMD 525797 doses of 750 and 1500mg every 3 wk were chosen. TRIAL REGISTRATION: NCT00958477 (EMR 62242-002).

[348]

TÍTULO / TITLE: - Promoter occupancy of MLL1 histone methyltransferase seems to specify the proliferative and apoptotic functions of E2F1 in a tumour microenvironment.

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

REVISTA / JOURNAL: - J Cell Sci. 2013 Jul 18.

●● [Enlace al texto completo \(gratis o de pago\) 1242/jcs.126235](#)

AUTORES / AUTHORS: - Swarnalatha M; Singh AK; Kumar V

RESUMEN / SUMMARY: - The E2F family of transcription factors are considered versatile modulators poised at biological crossroads to execute diverse cellular functions. Despite extensive studies on E2F, the molecular mechanisms that control specific biological functions of E2F1 transcription factor is still not fully understood. Here we have addressed the molecular underpinnings of paradoxical functions of E2F1 in a tumour microenvironment using the 'X15-myc' oncomouse model of hepatocellular carcinoma. We observed that the HBx oncoprotein of hepatitis B virus regulates E2F1 functions by interfering with its binding to Skp2 E3 ubiquitin ligase. The HBx-Skp2 interaction led to the accumulation of transcriptionally active E2F1 and histone methyltransferase mixed lineage leukemia 1 (MLL1) protein. During early stages of hepatocarcinogenesis, the increased E2F1 activity promoted cellular proliferation by stimulating the genes involved in cell cycle control and replication. However, during the late stages, E2F1 triggered replicational stress-induced DNA damage and sensitized cells to apoptotic death in a p53-independent manner. Interestingly, the differential promoter occupancy of MLL1 during the early and late stages of tumour development seemed to specify the

proliferative and apoptotic functions of E2F1 through its dynamic interaction with co-activator CBP or co-repressor Brg1. Thus, the temporally-regulated promoter occupancy of histone methyltransferase could be a novel regulatory mechanism associated with diverse cellular functions of E2F family of transcription factors.

[349]

TÍTULO / TITLE: - APRIL depletion induces cell cycle arrest and apoptosis through blocking TGF-beta1/ERK signaling pathway in human colorectal cancer cells.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Jul 20.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1766-](#)

[8](#)

AUTORES / AUTHORS: - Wang F; Chen L; Ni H; Wang G; Ding W; Cong H; Ju S; Yang S; Wang H

INSTITUCIÓN / INSTITUTION: - Department of Clinical Laboratory Center, Affiliated Hospital of Nantong University, School of Public Health, Nantong University, Nantong, 226001, Jiangsu, People's Republic of China.

RESUMEN / SUMMARY: - It is well documented that a proliferation-inducing ligand (APRIL), a newly found member of tumor necrosis factor superfamily, overexpressed in the majority of malignancies, plays a potential role in the occurrence and development of these tumors. Herein, we demonstrated that APRIL depletion by using RNA interference in human colorectal cancer (CRC) COLO 205 and SW480 cells resulted in cell proliferation inhibition and evoked cell cycle arrest in G0/G1 phase and apoptosis, coupled with decrease in CDK2, Cyclin D1, Bcl-2 expression and an increase of p21 and Bax expression. In addition, the decreased expression of transforming growth factor-beta1 (TGF-beta1) and p-ERK was also showed in siRNA-APRIL transfected COLO 205 and SW480 cells, whereas the protein expression levels of Smad2/3, p-Smad2/3, and ERK were not significantly changed. Taken together, our results indicate that APRIL depletion induces cell cycle arrest and apoptosis partly through blocking noncanonical TGF-beta1/ERK, rather than canonical TGF-beta1/Smad2/3, signaling pathway in CRC cells. Moreover, our study highlights APRIL as a potential molecular target for the therapy of CRC.

[350]

TÍTULO / TITLE: - A long non-coding RNA signature in glioblastoma multiforme predicts survival.

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

REVISTA / JOURNAL: - Neurobiol Dis. 2013 May 29;58C:123-131. doi: 10.1016/j.nbd.2013.05.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.nbd.2013.05.011](#)

AUTORES / AUTHORS: - Zhang XQ; Sun S; Lam KF; Kiang KM; Pu JK; Ho AS; Lui WM; Fung CF; Wong TS; Leung GK

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

RESUMEN / SUMMARY: - Long non-coding RNAs (lncRNAs) represent the leading edge of cancer research, and have been implicated in cancer biogenesis and prognosis. We aimed to identify lncRNA signatures that have prognostic values in glioblastoma multiforme (GBM). Using a lncRNA-mining approach, we performed lncRNA expression profiling in 213 GBM tumors from The Cancer Genome Atlas (TCGA), randomly divided into a training (n=107) and a testing set (n=106). We analyzed the associations between lncRNA signatures and clinical outcome in the training set, and validated the findings in the testing set. We also validated the identified lncRNA signature in another two independent GBM data sets from Gene Expression Omnibus (GEO), which contained specimens from 68 and 101 patients, respectively. We identified a set of six lncRNAs that were significantly associated with the overall survival in the training set ($P \leq 0.01$). Based on this six-lncRNA signature, the training-set patients could be classified into high-risk and low-risk subgroups with significantly different survival (HR=2.13, 95% CI=1.38-3.29; $P=0.001$). The prognostic value of this six-lncRNA signature was confirmed in the testing set and the two independent data sets. Further analysis revealed that the prognostic value of this signature was independent of age and O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. The identification of the prognostic lncRNAs indicates the potential roles of lncRNAs in GBM pathogenesis. This six-lncRNA signature may have clinical implications in the subclassification of GBM.

[351]

TÍTULO / TITLE: - Is ERCC1 a reliable prognostic protein biomarker in non-small-cell lung cancer?

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

REVISTA / JOURNAL: - Thorax. 2013 Jul 10. doi: 10.1136/thoraxjnl-2013-204086.

- Enlace al texto completo (gratis o de pago) [1136/thoraxjnl-2013-204086](#)

AUTORES / AUTHORS: - Durrington HJ

[352]

TÍTULO / TITLE: - The expression of fatty acid metabolism-associated proteins is correlated with the prognosis of meningiomas.

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

REVISTA / JOURNAL: - APMIS. 2013 Jul 24. doi: 10.1111/apm.12135.

- Enlace al texto completo (gratis o de pago) [1111/apm.12135](#)

AUTORES / AUTHORS: - Jiang J; Lin C; Liu N; Zhang Z; Sun Y; Fang X; Qi J

INSTITUCIÓN / INSTITUTION: - Department of Pathology, First Affiliated Hospital of Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - The expression of fatty acid metabolism-associated proteins is correlated with the prognosis of meningiomas. Meningioma is a common tumor of the nervous system; however, reliable prognostic markers for meningioma are currently insufficient. High fatty acid synthase (FAS) expression occurs in many tumors, and is associated with tumor progression and grade. Few studies have previously investigated fatty acid metabolism in meningioma; thus, in this study, we investigated the expression of FAS and brain fatty acid-binding protein (BFABP) proteins in all grades of meningioma and determined the association to meningioma grade, invasiveness, recurrence, and progression. We determined expression levels of FAS and BFABP in all grade meningiomas by immunohistochemical analysis in 314 patients diagnosed with meningioma. The expression levels of FAS and BFABP increased significantly in correlation with meningioma grade ($p < 0.01$). Compared with benign meningioma, the expression levels of FAS and BFABP were significantly higher in brain invasive meningioma ($p < 0.01$). Compared with nonrecurrent meningioma (benign meningioma), the expression of FAS was also increased in recurrent meningioma ($p < 0.01$). The expression of fatty acid metabolism-associated proteins potentially correlates with meningioma grade, invasiveness, aggressiveness, and recurrent status and provides evidence for a novel therapeutic target for meningioma.

[353]

TÍTULO / TITLE: - Histone deacetylase 4 mediates SMAD family member 4 deacetylation and induces 5-fluorouracil resistance in breast cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 1. doi: 10.3892/or.2013.2578.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2578](#)

AUTORES / AUTHORS: - Yu SL; Lee DC; Son JW; Park CG; Lee HY; Kang J

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, College of Medicine, Konyang University, Daejeon 302-718, Republic of Korea.

RESUMEN / SUMMARY: - Histone deacetylases (HDACs) have been shown to play important roles in the regulation of chromatin remodeling by histone deacetylation, and their expression is induced in several types of cancer. In addition, they are known to be associated with resistance to anticancer drugs. However, the relevance of HDAC4 in chemoresistance remains unclear. Therefore, we investigated the interaction between HDAC4 expression and chemoresistance in breast cancer cells. We found that increased HDAC4 expression in MDA-MB-231 cells was associated with resistance to the anticancer drug 5-fluorouracil (5-FU). To verify these results, a cell line stably overexpressing HDAC4 was generated using MCF-7 cells (HDAC4OE). This

cell line displayed increased 5-FU resistance, and HDAC4 knockdown in HDAC4OE cells restored 5-FU sensitivity. Consequently, we concluded that HDAC4 is a critical gene associated with 5FU chemoresistance. Further investigation using a microarray approach revealed that 355 genes were differentially expressed following HDAC4 overexpression. Based on functional annotation of the array results, HDAC4 overexpression was found to downregulate genes related to the transforming growth factor (TGF) beta signaling pathway, including SMAD4, SMAD6, bone morphogenetic protein 6, inhibitor of DNA binding 1 and TGFbeta2. We also found that HDAC4 expression regulates SMAD4 expression by inducing deacetylation of histone H3 in the SMAD4 promoter region. In addition, SMAD4 knockdown in MCF7 cells increased 5-FU resistance. In summary, our data suggest that HDAC4mediated deacetylation of the SMAD4 promoter may lead to 5-FU resistance in breast cancer cells.

[354]

TÍTULO / TITLE: - Synthetic phosphoethanolamine induces cell cycle arrest and apoptosis in human breast cancer MCF-7 cells through the mitochondrial pathway.

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

REVISTA / JOURNAL: - Biomed Pharmacother. 2013 Jul;67(6):481-7. doi: 10.1016/j.biopha.2013.01.012. Epub 2013 Feb 16.

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

1016/j.biopha.2013.01.012

AUTORES / AUTHORS: - Ferreira AK; Meneguelo R; Pereira A; Filho OM; Chierice GO; Maria DA

INSTITUCIÓN / INSTITUTION: - Biochemistry and Biophysical Laboratory, Butantan Institute, Sao Paulo, Brazil; Experimental Physiopathology, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - Phosphoethanolamine (Pho-s) is a compound involved in phospholipid turnover, acting as a substrate for many phospholipids of the cell membranes. In a recent study, we showed that Pho-s has antitumor effect in the several tumor cells. In this study we evaluated the antitumor activity of synthetic Pho-s on MCF-7 breast cancer cells. Here we demonstrate that Pho-s is cytotoxic to MCF-7 cells in a dose-dependent manner, while it is cytotoxic to MCF10 only at higher concentrations. In addition, Pho-s induces a disruption in mitochondrial membrane potential (Deltapsim). Furthermore, Pho-s induces mitochondria aggregates in the cytoplasm and DNA fragmentation of MCF-7 cells visualized by confocal microscopy. In agreement with the reduction on Deltapsim, we showed that Pho-s induces apoptosis followed by an increase in cytochrome c expression and capase-3-like activity in MCF-7 cells. Our results demonstrate that Pho-s induces a cell cycle arrest in the G1 phase through an inhibition of cyclin D1 and stimulates p53. An additional highlight of this study is

the finding that Pho-s inhibits Bcl-2, inducing apoptosis through the mitochondrial pathway. Taken together, these results show that Pho-s is a promising compound in the fight against cancer.

[355]

TÍTULO / TITLE: - LRIG1 dictates the chemo-sensitivity of temozolomide (TMZ) in U251 glioblastoma cells via down-regulation of EGFR/topoisomerase-2/Bcl-2.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 9. pii: S0006-291X(13)01126-1. doi: 10.1016/j.bbrc.2013.06.116.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.06.116

AUTORES / AUTHORS: - Qi XC; Xie DJ; Yan QF; Wang YR; Zhu YX; Qian C; Yang SX

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Sir Run Run Shaw Hospital, College of Medical Sciences, Zhejiang University, Hangzhou 310016, China.

RESUMEN / SUMMARY: - In the current study, we aimed to understand the potential role of leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1) in TMZ-resistance of U251 glioma cells. We established TMZ-resistant U251 clones (U251/TMZ cells), which expressed low level of LRIG1, but high levels of epidermal growth factor receptor (EGFR), topoisomerase-2 (Topo-2) and Bcl-2. Depletion of LRIG1 by the targeted RNA interference (RNAi) upregulated EGFR/Topo-2/Bcl-2 in U251 cells, and the cells were resistant to TMZ. Reversely, over-expression of LRIG1 in U251 cells downregulated EGFR/Topo-2/Bcl-2 expressions, and cells were hyper-sensitive to TMZ. Our data suggested EGFR-dependent mammalian target of rapamycin (mTOR) activation was important for Topo-2 and Bcl-2 expressions in U251/TMZ cells. The EGFR inhibitor and the mTOR inhibitor downregulated Topo-2/Bcl-2 expressions, both inhibitors also restored TMZ sensitivity in U251/TMZ cells. Finally, inhibition of Topo-2 or Bcl-2 by targeted RNAi(s) knockdown or by the corresponding inhibitor re-sensitized U251/TMZ cells to TMZ, indicating that both Topo-2 and Bcl-2 were important for TMZ resistance in the resistant U251 cells. Based on these results, we concluded that LRIG1 inhibits EGFR expression and the downstream signaling activation, interferes with Bcl-2/Topo-2 expressions and eventually sensitizes glioma cells to TMZ.

[356]

TÍTULO / TITLE: - Phospho-DeltaNp63alpha-dependent microRNAs modulate chemoresistance of squamous cell carcinoma cells to cisplatin: At the crossroads of cell life and death.

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

REVISTA / JOURNAL: - FEBS Lett. 2013 Jul 2. pii: S0014-5793(13)00467-5. doi: 10.1016/j.febslet.2013.06.020.

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

1016/j.febslet.2013.06.020

AUTORES / AUTHORS: - Ratovitski EA

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology/Head and Neck Surgery, The Johns Hopkins School of Medicine, Baltimore, MD 21231, USA. Electronic address: eratovi1@jhmi.edu.

RESUMEN / SUMMARY: - The tumor protein p63/microRNA functional network appears to play a decisive role in chemoresistance of human epithelial cancers. The cisplatin- and phosphorylated-DeltaNp63alpha-dependent microRNAs, whose expression was varied in sensitive and resistant squamous cell carcinoma cells (SCC, which were derived from larynx and tongue tumors), were shown to modulate the expression of multiple members of cell cycle arrest, apoptosis and autophagy pathways. The specific microRNAs were further shown to modulate the resistant phenotype of SCC cells in vitro, thereby providing groundwork for novel chemotherapeutic venues for head and neck cancer.

[357]

TÍTULO / TITLE: - Repression of NR4A1 by a chromatin modifier promotes docetaxel resistance in PC-3 human prostate cancer cells.

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

REVISTA / JOURNAL: - FEBS Lett. 2013 Jul 2. pii: S0014-5793(13)00487-0. doi: 10.1016/j.febslet.2013.06.029.

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

1016/j.febslet.2013.06.029

AUTORES / AUTHORS: - Yu L; Su YS; Zhao J; Wang H; Li W

INSTITUCIÓN / INSTITUTION: - Department of Urology, Xijing Hospital, Fourth Military Medical University, No. 127 Changle West Road, Xi'an 710032, China; Department of Urology, 3rd Hospital of PLA, No. 45 Dongfeng Road, Bao Ji 721004, China.

RESUMEN / SUMMARY: - Epigenetic silencing mechanisms play an important role in chemoresistance of human cancer. Here we report the upregulated expression of metastasis-associated protein 1 (MTA1), a component of the nucleosome remodeling deacetylation (NuRD) complex, in chemoresistant prostate cancer (PCa). MTA1 knockdown in PC-3 cells inhibited cell proliferation and enhanced docetaxel (DTX)-induced cell death. Conversely, overexpression of MTA1 promotes DTX chemoresistance in PC-3 cells. MTA1 acted as a potent corepressor of the nuclear receptor NR4A1 transcription by interacting with histone deacetylase 2 (HDAC2). These findings suggest that MTA1 may serve as a novel DTX-resistance promoter in PC-3 cells.

[358]

TÍTULO / TITLE: - Toll-like Receptor-4 Expression by Stromal Fibroblasts Is Associated With Poor Prognosis in Colorectal Cancer.

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

REVISTA / JOURNAL: - J Immunother. 2013 Jul-Aug;36(6):342-9. doi: 10.1097/CJI.0b013e31829d85e6.

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

[1097/CJI.0b013e31829d85e6](#)

AUTORES / AUTHORS: - Eiro N; Gonzalez L; Gonzalez LO; Fernandez-Garcia B; Andicoechea A; Barbon E; Garcia-Muniz JL; Vizoso FJ

INSTITUCIÓN / INSTITUTION: - *Unidad de Investigacion daggerServicio de Anatomia Patologica double daggerServicio de Cirugia General, Fundacion Hospital de Jove, Gijon, Asturias, España.

RESUMEN / SUMMARY: - Because of the important role in inflammation and tissue regeneration, toll-like receptors (TLR) are likely candidates to mediate effects of the innate immune system on tumorigenesis. The aim of this study was to investigate the expression and clinical relevance of TLR in colorectal cancer (CRC). The expressions of TLR3, TLR4, TLR7, and TLR9 were analyzed in 104 patients with resectable CRC by immunohistochemistry. The evaluation of the expression consisted on measuring the overall level of TLR expression and by each cell type. The results showed a direct association between the histologic grade of tumor and TLR9 expression by tumor cells. TLR4 expression by tumor cells was significantly associated with a lower rate of tumor recurrence, whereas the expression by fibroblasts was significant and independently associated with a high rate of tumor recurrence and with a shortened overall survival in patients; particularly in tumors from left colon and rectum. Therefore, TLR4 expression by fibroblasts could be a useful prognostic marker in CRC.

[359]

TÍTULO / TITLE: - Synergistically killing activity of aspirin and histone deacetylase inhibitor valproic acid (VPA) on hepatocellular cancer cells.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jun 28;436(2):259-64. doi: 10.1016/j.bbrc.2013.05.088. Epub 2013 May 30.

●● Enlace al texto completo (gratis o de pago) [1016/j.bbrc.2013.05.088](#)

AUTORES / AUTHORS: - Li X; Zhu Y; He H; Lou L; Ye W; Chen Y; Wang J

INSTITUCIÓN / INSTITUTION: - Department of Infectious Diseases, Yiwu Central Hospita, 519 Nan men Street, Yiwu, Jinhua, Zhejiang 322000, China.

RESUMEN / SUMMARY: - Aspirin and valproic acid (VPA) have been extensively studied for inducing various malignancies growth inhibition respectively, despite their severe side effects. Here, we developed a novel combination by aspirin

and VPA on hepatocellular cancer cells (HCCs). The viability of HCC lines were analyzed by MTT assay, apoptotic analysis of HepG2 and SMMC-7721 cell was performed. Real time-PCR and Western blotting were performed to determine the expression of apoptosis related genes and proteins such as Survivin, Bcl-2/Bax, Cyclin D1 and p15. Moreover, orthotopic xenograft tumors were challenged in nude mice to establish murine model, and then therapeutic effect was analyzed after drug combination therapy. The viability of HCC lines' significantly decreased after drug combination treatment, and cancer cell apoptosis in combination group increasingly induced compared with single drug use. Therapeutic effect was significantly enhanced by combination therapy in tumor volume and tumor weight decrease. From the data shown here, aspirin and VPA combination have a synergistic killing effect on hepatocellular cancers cells proliferation and apoptosis.

[360]

TÍTULO / TITLE: - Androgen metabolite-dependent growth of hormone receptor-positive breast cancer as a possible aromatase inhibitor-resistance mechanism.

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

REVISTA / JOURNAL: - Breast Cancer Res Treat. 2013 Jun;139(3):731-40. doi: 10.1007/s10549-013-2595-x. Epub 2013 Jun 19.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10549-013-2595-](#)

[X](#)

AUTORES / AUTHORS: - Hanamura T; Niwa T; Nishikawa S; Konno H; Gohno T; Tazawa C; Kobayashi Y; Kurosumi M; Takei H; Yamaguchi Y; Ito K; Hayashi S

INSTITUCIÓN / INSTITUTION: - Department of Molecular and Functional Dynamics, Graduate School of Medicine, Tohoku University, 2-1 Seiryomachi, Aoba-ku, Sendai, 980-8575, Japan, hanamura@shinshu-u.ac.jp.

RESUMEN / SUMMARY: - Aromatase inhibitors (AIs) have been reported to exert their antiproliferative effects in postmenopausal women with hormone receptor-positive breast cancer not only by reducing estrogen production but also by unmasking the inhibitory effects of androgens such as testosterone (TS) and dihydrotestosterone (DHT). However, the role of androgens in AI-resistance mechanisms is not sufficiently understood. 5 α -Androstane-3 β ,17 β -diol (3 β -diol) generated from DHT by 3 β -hydroxysteroid dehydrogenase type 1 (HSD3B1) shows androgenic and substantial estrogenic activities, representing a potential mechanism of AI resistance. Estrogen response element (ERE)-green fluorescent protein (GFP)-transfected MCF-7 breast cancer cells (E10 cells) were cultured for 3 months under steroid-depleted, TS-supplemented conditions. Among the surviving cells, two stable variants showing androgen metabolite-dependent ER activity were selected by monitoring GFP expression. We investigated the process of adaptation to androgen-abundant conditions and the role of androgens in AI-resistance mechanisms in these variant cell lines. The variant cell lines showed increased

growth and induction of estrogen-responsive genes rather than androgen-responsive genes after stimulation with androgens or 3beta-diol. Further analysis suggested that increased expression of HSD3B1 and reduced expression of androgen receptor (AR) promoted adaptation to androgen-abundant conditions, as indicated by the increased conversion of DHT into 3beta-diol by HSD3B1 and AR signal reduction. Furthermore, in parental E10 cells, ectopic expression of HSD3B1 or inhibition of AR resulted in adaptation to androgen-abundant conditions. Coculture with stromal cells to mimic local estrogen production from androgens reduced cell sensitivity to AIs compared with parental E10 cells. These results suggest that increased expression of HSD3B1 and reduced expression of AR might reduce the sensitivity to AIs as demonstrated by enhanced androgen metabolite-induced ER activation and growth mechanisms. Androgen metabolite-dependent growth of breast cancer cells may therefore play a role in AI-resistance.

[361]

TÍTULO / TITLE: - Quantification of a Proteotypic Peptide from Protein C Inhibitor by Liquid Chromatography-Free SISCAPA-MALDI Mass Spectrometry: Application to Identification of Recurrence of Prostate Cancer.

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

REVISTA / JOURNAL: - Clin Chem. 2013 Jul 15.

- Enlace al texto completo (gratis o de pago)

[1373/clinchem.2012.199786](#)

AUTORES / AUTHORS: - Razavi M; Johnson LD; Lum JJ; Kruppa G; Anderson NL; Pearson TW

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Microbiology, University of Victoria, Victoria, British Columbia, Canada;

RESUMEN / SUMMARY: - BACKGROUND: Biomarker validation remains one of the most challenging constraints to the development of new diagnostic assays. To facilitate biomarker validation, we previously developed a chromatography-free stable isotope standards and capture by antipeptide antibodies (SISCAPA)-MALDI assay allowing rapid, high-throughput quantification of protein analytes in large sample sets. Here we applied this assay to the measurement of a surrogate proteotypic peptide from protein C inhibitor (PCI) in sera from patients with prostate cancer. METHODS: A 2-plex SISCAPA-MALDI assay for quantification of proteotypic peptides from PCI and soluble transferrin receptor (sTfR) was used to measure these peptides in 159 trypsin-digested sera collected from 51 patients with prostate cancer. These patients had been treated with radiation with or without neoadjuvant androgen deprivation. RESULTS: Patients who experienced biochemical recurrence of prostate cancer showed decreased serum concentrations of the PCI peptide analyte within 18 months of treatment. The PCI peptide concentrations remained increased in the sera of patients who did not experience cancer

recurrence. Prostate-specific antigen concentrations had no predictive value during the same time period. CONCLUSIONS: The high-throughput, liquid chromatography-free SISCAPA-MALDI assay is capable of rapid quantification of proteotypic PCI and sTfR peptide analytes in complex serum samples. Decreased serum concentrations of the PCI peptide were found to be related to recurrence of prostate cancer in patients treated with radiation with or without hormone therapy. However, a larger cohort of patients will be required for unequivocal validation of the PCI peptide as a biomarker for clinical use.

[362]

TÍTULO / TITLE: - Cytoplasmic expression of the ELAV-like protein HuR as a potential prognostic marker in esophageal squamous cell carcinoma.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jul 20.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-1008-](#)

[4](#)

AUTORES / AUTHORS: - Zhang C; Xue G; Bi J; Geng M; Chu H; Guan Y; Wang J; Wang B

INSTITUCIÓN / INSTITUTION: - Department of Oncology, General Hospital, Jinan Command of the People's Liberation Army, Shifan Street 25, Tianqiao District, Jinan, 250031, China.

RESUMEN / SUMMARY: - Esophageal squamous cell carcinoma (ESCC) is one of the most frequent cancers and a leading cause of death from cancer in China. The human ELAV-like protein HuR has been found to contribute to cancer development and progression through stabilizing a group of cellular mRNAs of cancer-related genes. In this study, we investigated the expression of HuR in a cohort of ESCC patients using immunohistochemical staining. HuR detected in the cytoplasm of cancer cells was positive in 46.6 % of 58 ESCC specimens; 75.9 % of these specimens had nuclear immunoreactivity for HuR. Cytoplasmic HuR expression was higher in cancer tissues compared to 20 matched adjacent noncancerous tissues. A clinicopathological study showed that cytoplasmic HuR expression was positively associated with lymph node metastasis, depth of tumor invasion, and advanced stage, whereas nuclear HuR expression was not correlated with any clinicopathological factors. Patients positive for cytoplasmic HuR expression had a cumulative 5-year survival rate of 25.3 %, whereas it was 43.8 % for patients negative for cytoplasmic HuR expression. In a multivariate analysis, cytoplasmic HuR expression was an independent prognostic factor, whereas nuclear positivity for HuR was not. Our results indicate that high cytoplasmic HuR expression is associated with positive lymph node metastasis, deep tumor invasion, high stage, and poor survival in ESCC. Thus, HuR is the first mRNA stability protein whose expression is associated with poor survival in esophageal cancer.

[363]

TÍTULO / TITLE: - Cavin-1 is essential for the tumor-promoting effect of caveolin-1 and enhances its prognostic potency in pancreatic cancer.

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

REVISTA / JOURNAL: - Oncogene. 2013 Jun 17. doi: 10.1038/onc.2013.223.

●● Enlace al texto completo (gratis o de pago) [1038/onc.2013.223](#)

AUTORES / AUTHORS: - Liu L; Xu HX; Wang WQ; Wu CT; Chen T; Qin Y; Liu C; Xu J; Long J; Zhang B; Xu YF; Ni QX; Li M; Yu XJ

INSTITUCIÓN / INSTITUTION: - Pancreatic Cancer Institute, Fudan University; Department of Pancreatic and Hepatobiliary Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China.

RESUMEN / SUMMARY: - Caveolin-1 exhibits a stage-dependent, functional fluctuation during pancreatic cancer development, but the underlying mechanisms remain unclear. Here, we report that cavin-1, a structural protein of caveolae, modulates the oncogenic function of caveolin-1 and cooperates with caveolin-1 to enhance pancreatic cancer aggressiveness. Cavin-1 expression is associated with caveolin-1 in pancreatic cancer tissue samples and cell lines, and predicts the metastatic potential of pancreatic cancer. Interactome analyses further revealed the physical interaction of cavin-1 and caveolin-1 and their colocalization in pancreatic cancer cells. Cavin-1 stabilizes caveolin-1 expression or activity by inhibiting its internalization and subsequent lysosomal degradation. More in-depth functional experiments showed that caveolin-1-enhanced aggressiveness of pancreatic cancer cells is dependent on the presence of cavin-1. In contrast, cavin-1 depletion inhibited the invasion and metastasis of pancreatic cancer cells, which could not be restored by caveolin-1-rescue construct. Tissue microarray analyses in two independent clinic cohorts also supported the augment of cavin-1 on the prognostic potency of caveolin-1, and showed that combination of cavin-1 with caveolin-1 predicted worse survival in pancreatic cancer patients. Of note, the phenotypes because of cavin-1 could not be achieved by other cavins such as cavin-2, and the tumor-promoting role of cavin-1 in pancreatic cancer was found to be largely dependent on caveolin-1 expression, which highlights the critical role of cavin-1/caveolin-1 in pancreatic cancer progression, and suggests that the interruption of cavin-1/caveolin-1 interaction is a promising therapeutic strategy for pancreatic cancer. Oncogene advance online publication, 17 June 2013; doi:10.1038/onc.2013.223.

[364]

TÍTULO / TITLE: - A miR-146^a Polymorphism (rs2910164) Predicts Risk of and Survival from Colorectal Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3233-9.

AUTORES / AUTHORS: - Chae YS; Kim JG; Lee SJ; Kang BW; Lee YJ; Park JY; Jeon HS; Park JS; Choi GS

INSTITUCIÓN / INSTITUTION: - Kyungpook National University Medical Center, Kyungpook National University School of Medicine, 807 Hogukno, Buk-Gu, Daegu 702-210, Korea. Tel: +82 532003521, jkk21c@knu.ac.kr.

RESUMEN / SUMMARY: - **BACKGROUND:** Recent evidence suggests that the rs2910164 variant of miR-146^a is associated with the development of certain types of cancer. Therefore, the aim of this study was to investigate the association of this genetic variant with susceptibility and prognosis in patients with colorectal cancer (CRC). **MATERIALS AND METHODS:** Genotyping analyses of miR-146^a rs2690164 for risk and survival in CRC were performed in a case-control study (n=967) using a polymerase chain reaction (PCR)-restriction fragment length polymorphism assay. **RESULTS:** The C allelic frequency of miR-146 rs2690164 in the 399 patients and 568 controls was 61.9% and 53.9%, respectively. In the case-control study, those who possessed the CC genotype had a higher risk of CRC compared to those with the CG or GG genotype (odds ratio=1.569; 95% confidence interval=1.196-2.059; p=0.001), regardless of the tumor site. In the survival analysis of 343 patients with CRC who underwent curative surgery, those with CC genotype had a worse survival outcome compared with those with CG or GG genotype in a Kaplan-Meier survival analysis. Moreover, a multivariate analysis showed that the CC genotype of miR-146^a rs2910164 was associated with worse relapse-free and disease-specific survival compared to the CG or GG genotype in a recessive model of the C allele, adjusted for patient and tumor characteristics (hazard ratio=2.120 and 2.349, p=0.005 and 0.007, respectively). **CONCLUSION:** The current study provides evidence that the miR-146^a rs2690164 polymorphism, as the dominant model of the G allele, is associated with the susceptibility and prognosis of CRC.

[365]

TÍTULO / TITLE: - The prognostic significance of aldehyde dehydrogenase 1^{a1} (ALDH1A1) and CD133 expression in early stage non-small cell lung cancer.

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

REVISTA / JOURNAL: - Thorax. 2013 Aug 7. doi: 10.1136/thoraxjnl-2012-203021.

●● Enlace al texto completo (gratis o de pago) [1136/thoraxjnl-2012-203021](#)

AUTORES / AUTHORS: - Alamgeer M; Ganju V; Szczepny A; Russell PA; Prodanovic Z; Kumar B; Wainer Z; Brown T; Schneider-Kolsky M; Conron M; Wright G; Watkins DN

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Monash Medical Centre, , East Bentleigh, Melbourne, Australia.

RESUMEN / SUMMARY: - BACKGROUND: Expression of aldehyde dehydrogenase 1^{a1} (ALDH1A1) and CD133 has been functionally associated with a stem cell phenotype in normal and malignant cells. The prevalence of such cells in solid tumours should therefore correlate with recurrence and/or metastasis following definitive surgical resection. The aim of this study was to evaluate the prognostic significance of ALDH1A1 and CD133 in surgically resected, early stage non-small cell lung cancer (NSCLC). METHODS: A retrospective analysis of ALDH1A1 and CD133 expression in 205 patients with pathologic stage I NSCLC was performed using immunohistochemistry. The association between the expression of both markers and survival was determined. RESULTS: We identified 62 relapses and 58 cancer-related deaths in 144 stage 1^a and 61 stage 1B patients, analysed at a median of 5-years follow-up. Overexpression of ALDH1A1 and CD133, detected in 68.7% and 50.7% of primary tumours, respectively, was an independent prognostic indicator for overall survival by multivariable Cox proportional hazard model (p=0.017 and 0.039, respectively). Overexpression of ALDH1A1, but not of CD133, predicted poor recurrence-free survival (p=0.025). When categorised into three groups according to expression of ALDH1A1/CD133, patients with overexpression of both ALDH1A1 and CD133 belonged to the group with the shortest recurrence-free and overall survival (p=0.015 and 0.017, respectively). CONCLUSIONS: Expression of ALDH1A1 and CD133, and coexpression of ALDH1A1 and CD133, is strongly associated with poor survival in early-stage NSCLC following surgical resection. These data are consistent with the hypothesis that expression of stem cell markers correlates with recurrence as an indirect measure of self-renewal capacity.

[366]

TÍTULO / TITLE: - Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma.

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

REVISTA / JOURNAL: - Radiother Oncol. 2013 May 30. pii: S0167-8140(13)00224-7. doi: 10.1016/j.radonc.2013.05.011.

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

[1016/j.radonc.2013.05.011](#)

AUTORES / AUTHORS: - Cattaneo GM; Passoni P; Longobardi B; Slim N; Reni M; Cereda S; di Muzio N; Calandrino R

INSTITUCIÓN / INSTITUTION: - Medical Physics Department, San Raffaele Scientific Institute, Milan, Italy. Electronic address: cattaneo.mauro@hsr.it.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Hypofractionated radiotherapy (RT) of pancreatic adenocarcinoma is limited by the tolerance of adjacent normal tissues. A better understanding of the influence of dosimetric variables on the rate of toxicity after RT must be considered an important goal.

METHODS AND MATERIALS: Sixty-one patients with histologically proven locally advanced disease (LAPD) were analyzed. The therapeutic strategy consisted of induction chemotherapy (ChT) followed by concurrent chemoradiotherapy (CRT). In 39 out of 61 patients the target volume was based on a four-dimensional CT (4D-CT) procedure. Delivered dose was 44.25Gy in 15 fractions to PTV2, which consisted of pancreatic tumor and regional lymph nodes considered radiologically involved; 23 out of 61 patients received a simultaneous integrated boost (SIB) to a tumor sub-volume infiltrating the great abdominal vessels (PTV1) with dose in the range of 48-58Gy. RT was delivered with Helical Tomotherapy. Dose-volume histograms (DVHs) of target volumes and organs at risk (OARs) were collected for analysis. The predictive value of clinical/dosimetric parameters was tested by univariate/multivariate analyses. **RESULTS:** The crude incidence of acute gastrointestinal (GI) grade 2 toxicity was 33%. The 12-month actuarial rate of “anatomical” (gastro-duodenal mucosa damage) toxicity was 13% (95% CI: 4-22%). On univariate analysis, several stomach and duodenum DVH endpoints are predictive of toxicity after moderately hypofractionated radiotherapy. Multivariate analysis confirmed that baseline performance status and the stomach V20[%] were strong independent predictors of acute GI grade 2 toxicity. The high-dose region of duodenum DVH (V45[%]; V40[%]) was strongly correlated with grade 2 “anatomical” toxicity; the best V40[%] and V45[%] cut-off values were 16% and 2.6% respectively. **CONCLUSION:** Regarding dosimetric indices, stomach V20[%] correlates with a higher rate of acute toxicity; more severe acute and late anatomical toxicities are related to the high dose region of duodenum DVH.

[367]

TÍTULO / TITLE: - Evidence of a role for CD44 and cell adhesion in mediating resistance to lenalidomide in multiple myeloma: therapeutic implications.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jun 13. doi: 10.1038/leu.2013.174.

●● [Enlace al texto completo \(gratis o de pago\) 1038/leu.2013.174](#)

AUTORES / AUTHORS: - Bjorklund CC; Baladandayuthapani V; Lin HY; Jones RJ; Kuitse I; Wang H; Yang J; Shah JJ; Thomas SK; Wang M; Weber DM; Orłowski RZ

INSTITUCIÓN / INSTITUTION: - Department of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

RESUMEN / SUMMARY: - Resistance of myeloma to lenalidomide is an emerging clinical problem, and though it has been associated in part with activation of Wnt/beta-catenin signaling, the mediators of this phenotype remained undefined. Lenalidomide-resistant models were found to overexpress the hyaluronan (HA)-binding protein CD44, a downstream Wnt/beta-catenin transcriptional target. Consistent with a role of CD44 in cell adhesion-mediated drug resistance (CAM-DR), lenalidomide-resistant myeloma cells were more

adhesive to bone marrow stroma and HA-coated plates. Blockade of CD44 with monoclonal antibodies, free HA or CD44 knockdown reduced adhesion and sensitized to lenalidomide. Wnt/beta-catenin suppression by FH535 enhanced the activity of lenalidomide, as did interleukin-6 neutralization with siltuximab. Notably, all-trans retinoic acid (ATRA) downregulated total beta-catenin, cell-surface and total CD44, reduced adhesion of lenalidomide-resistant myeloma cells and enhanced the activity of lenalidomide in a lenalidomide-resistant in vivo murine xenograft model. Finally, ATRA sensitized primary myeloma samples from patients that had relapsed and/or refractory disease after lenalidomide therapy to this immunomodulatory agent ex vivo. Taken together, our findings support the hypotheses that CD44 and CAM-DR contribute to lenalidomide resistance in multiple myeloma, that CD44 should be evaluated as a putative biomarker of sensitivity to lenalidomide, and that ATRA or other approaches that target CD44 may overcome clinical lenalidomide resistance. Leukemia advance online publication, 26 July 2013; doi:10.1038/leu.2013.174.

[368]

TÍTULO / TITLE: - Sequential Treatment of Advanced-stage Lung Adenocarcinoma Harboring Wild-type EGFR Gene: Second-line Pemetrexed Followed by Third-line Erlotinib versus the Reverse Sequence.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3397-402.

AUTORES / AUTHORS: - Fiala O; Pesek M; Finek J; Benesova L; Bortlicek Z; Minarik M

INSTITUCIÓN / INSTITUTION: - MUDr., Department of Oncology and Radiotherapy, Medical School and Teaching Hospital in Pilsen, Charles University in Prague, alej Svobody 80, CZ-304 60 Pilsen, Czech Republic. fiala.o@centrum.cz.

RESUMEN / SUMMARY: - BACKGROUND: Pemetrexed and erlotinib represent novel agents for the treatment of non-small cell lung cancer (NSCLC). The role of sequential treatment in NSCLC has not been elucidated yet. We compared the efficacy of second-line pemetrexed followed by third-line erlotinib (P-E) to treatment with the reverse sequence (E-P). PATIENTS AND METHODS: We analyzed data of 57 patients with advanced-stage (IIIB/IV) lung adenocarcinoma harboring wild-type epidermal growth factor receptor (EGFR) gene; 31 patients were treated with P-E and 26 patients with the E-P sequence. RESULTS: The median progression-free survival (PFS) for patients treated with P-E was 3.6 months vs. 7.8 months for patients treated with E-P ($p=0.029$). The median overall survival (OS) for patients treated with P-E was 7.9 months vs. 26.3 months for patients treated with E-P ($p=0.006$). CONCLUSION: The results proved a significant improvement of both PFS and OS for patients treated with the E-P sequence as compared to the P-E sequence.

[369]

TÍTULO / TITLE: - Evidence of epidermal growth factor receptor expression in uveal melanoma: Inhibition of epidermal growth factor-mediated signalling by Gefitinib and Cetuximab triggered antibody-dependent cellular cytotoxicity.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jul 9. pii: S0959-8049(13)00486-3. doi: 10.1016/j.ejca.2013.06.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.ejca.2013.06.011](#)

AUTORES / AUTHORS: - Amaro A; Mirisola V; Angelini G; Musso A; Tosetti F; Esposito AI; Perri P; Lanza F; Nasciuti F; Mosci C; Puzone R; Salvi S; Truini M; Poggi A; Pfeffer U

INSTITUCIÓN / INSTITUTION: - Integrated Molecular Pathology, IRCCS A.O.U. San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.

RESUMEN / SUMMARY: - Despite advances in surgery and radiotherapy of uveal melanoma (UM), many patients develop distant metastases that poorly respond to therapy. Improved therapies for the metastatic disease are therefore urgently needed. Expression of the epidermal growth factor receptor (EGFR), a target of kinase inhibitors and humanised antibodies in use for several cancers, had been reported. Forty-eight human UMs were analysed by expression profiling. Signalling was tested in three EGFR expressing UM cell lines by Western blotting using phosphorylation specific antibodies for EGFR and the downstream mediators AKT (v-akt murine thymoma viral oncogene homolog) and extracellular signal-regulated kinase (ERK). Evidence for signalling in tumours was obtained through the application of a UM-specific EGF-signature. The EGFR specific kinase inhibitor, Gefitinib and the humanised monoclonal antibody, Cetuximab, were tested for their effect on EGFR signalling. Natural killer cell mediated antibody-dependent cellular cytotoxicity (ADCC) and tumour necrosis factor alpha (TNF-alpha) release was analysed for Cetuximab. Fourteen of 48 UMs and three of 14 cell lines (over-)express EGFR, at least in part due to trisomy of the EGFR locus on chromosome 7p12. EGFR and the downstream mediator, AKT, are phosphorylated upon stimulation with EGF in EGFR expressing cell lines. EGFR over-expressing tumours but not EGFR negative tumours show an activated EGF-signature. Gefitinib inhibits EGFR and AKT phosphorylation and Cetuximab induces EGFR phosphorylation but inhibits signalling to AKT induced with EGF. Cetuximab triggers natural killer (NK) cells to lyse EGFR+ cell lines and to release TNF-alpha. EGFR appears suited as a novel molecular drug target for therapy of uveal melanoma.

[370]

TÍTULO / TITLE: - Distribution and prognosis of molecular breast cancer subtypes defined by immunohistochemical biomarkers in a Spanish population-based study.

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

REVISTA / JOURNAL: - Gynecol Oncol. 2013 Jun 6. pii: S0090-8258(13)00828-7. doi: 10.1016/j.ygyno.2013.05.039.

- Enlace al texto completo (gratis o de pago)

[1016/j.ygyno.2013.05.039](#)

AUTORES / AUTHORS: - Puig-Vives M; Sanchez MJ; Sanchez-Cantalejo J; Torrella-Ramos A; Martos C; Ardanaz E; Chirlaque MD; Perucha J; Diaz JM; Mateos A; Machon M; Marcos-Gragera R

INSTITUCIÓN / INSTITUTION: - Epidemiology Unit and Girona Cancer Registry (UERCG), Girona, España; Girona Biomedical Research Institute (IdIBGi), Girona, España; Research Group on Statistics, Econometrics and Health (GRECS), Universitat de Girona, Girona, España; CIBER of Epidemiology and Public Health (CIBERESP), España. Electronic address:

mpuig.icogirona@gmail.com.

RESUMEN / SUMMARY: - BACKGROUND: The objective of this study is to analyze the distribution, clinicopathological features, relative survival rate and excess risk of death among females diagnosed with invasive breast cancer and classified by molecular subtype from ten Spanish cancer registries. METHOD: Three thousand four hundred and eighty incident cases of women - mostly diagnosed in 2005 - were classified into five molecular subtypes according to immunohistochemical status of hormonal receptors and HER2 (human epidermal growth factor receptor 2): estrogen receptor (ER) and/or progesterone receptor (PR)+ and HER2-, ER+ and/or PR+ and HER2+, HER2-overexpressed (ER-, PR- and HER2+), triple negative (ER, PR and HER2-) and unclassified (hormonal receptor or/and HER2 unknown). Relative survival rates at 1, 3 and 5 years and relative excess risks (RER) of death adjusting for molecular subtype, age, stage and histological grade were estimated. RESULTS: Marked differences in clinicopathological characteristics and relative survival rate were observed between molecular subtypes. Compared with women with ER+ and/or PR+ and HER2-, ER+ and/or PR+ and HER2+ cases had an RER of 1.00 (95% CI: 0.66 to 1.52) after adjusting for age, stage and histological grade, whereas HER2-overexpressed, triple negative and women with unclassified subtypes presented an RER of 1.72 (95% CI: 1.15 to 2.57), 3.16 (95% CI: 2.26 to 4.41) and 2.55 (95% CI: 1.96 to 3.32), respectively. CONCLUSION: The prognostic value of molecular subtype persists when adjusting for age, stage and histological grade. Hormone receptor-positive tumors were associated with a better prognosis when compared with HER2-overexpressed and triple negative subtypes. Further research is required to improve triple negative prognosis.

[371]

TÍTULO / TITLE: - Steroidal aromatase inhibitors inhibit growth of hormone-dependent breast cancer cells by inducing cell cycle arrest and apoptosis.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0879-](#)

[6](#)

AUTORES / AUTHORS: - Amaral C; Varela C; Borges M; Tavares da Silva E; Roleira FM; Correia-da-Silva G; Teixeira N

INSTITUCIÓN / INSTITUTION: - Laboratory of Biochemistry, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, no. 228, 4050-313, Porto, Portugal.

RESUMEN / SUMMARY: - Different hormonal therapies are used for estrogen receptor positive (ER+) breast cancers, being the third-generation of aromatase inhibitors (AIs), an effective alternative to the classical tamoxifen. AIs inhibit the enzyme aromatase, which is responsible for catalyzing the conversion of androgens to estrogens. In this study, it was evaluated the effects of several steroidal AIs, namely 3beta-hydroxyandrost-4-en-17-one (1), androst-4-en-17-one (12), 4alpha,5alpha-epoxyandrostan-17-one (13^a) and 5alpha-androst-2-en-17-one (16), on cell proliferation, cell cycle progression and cell death in an ER+ aromatase-overexpressing human breast cancer cell line (MCF-7aro). All AIs induced a decrease in cell proliferation and these anti-proliferative effects were due to a disruption in cell cycle progression and cell death, by apoptosis. AIs 1 and 16 caused cell cycle arrest in G0/G1, while AIs 12 and 13^a induced an arrest in G2/M. Moreover, it was observed that these AIs induced apoptosis by different pathways, since AIs 1, 12 and 13^a activated the apoptotic mitochondrial pathway, while AI 16 induced apoptosis through activation of caspase-8. These results are important for the elucidation of the cellular effects of steroidal AIs on breast cancer cells and will also highlight the importance of AIs as inducers of apoptosis in hormone-dependent breast cancers.

[372]

TÍTULO / TITLE: - Targeting cancer stem cells in glioblastoma multiforme using mTOR inhibitors and the differentiating agent all-trans retinoic acid.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 18. doi: 10.3892/or.2013.2625.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2625](#)

AUTORES / AUTHORS: - Friedman MD; Jeevan DS; Tobias M; Murali R; Jhanwar-Uniyal M

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, New York Medical College, Valhalla, NY 10595, USA.

RESUMEN / SUMMARY: - Glioblastoma multiforme (GBM), the most aggressive primary brain tumor, portends a poor prognosis despite current treatment

modalities. Recurrence of tumor growth is attributed to the presence of treatment-resistant cancer stem cells (CSCs). The targeting of these CSCs is therefore essential in the treatment of this disease. Mechanistic target of rapamycin (mTOR) forms two multiprotein complexes, mTORC1 and mTORC2, which regulate proliferation and migration, respectively. Aberrant function of mTOR has been shown to be present in GBM CSCs. All-trans retinoic acid (ATRA), a derivative of retinol, causes differentiation of CSCs as well as normal neural progenitor cells. The purpose of this investigation was to delineate the role of mTOR in CSC maintenance, and to establish the mechanism of targeting GBM CSCs using differentiating agents along with inhibitors of the mTOR pathways. The results demonstrated that ATRA caused differentiation of CSCs, as demonstrated by the loss of the stem cell marker Nestin. These observations were confirmed by western blotting, which demonstrated a time-dependent decrease in Nestin expression following ATRA treatment. This effect occurred despite combination with mTOR (rapamycin), PI3K (LY294002) and MEK1/2 (U0126) inhibitors. Expression of activated extracellular signal-regulated kinase 1/2 (pERK1/2) was enhanced following treatment with ATRA, independent of mTOR pathway inhibitors. Proliferation of CSCs, determined by neurosphere diameter, was decreased following treatment with ATRA alone and in combination with rapamycin. The motility of GBM cells was mitigated by treatment with ATRA, rapamycin and LY29002 alone. However, combination treatment augmented the inhibitory effect on migration suggesting synergism. These findings indicate that ATRA-induced differentiation is mediated via the ERK1/2 pathway, and underscores the significance of including differentiating agents along with inhibitors of mTOR pathways in the treatment of GBM.

[373]

TÍTULO / TITLE: - Genistein modulates oxidative stress in breast cancer cell lines according to ERalpha/ERbeta ratio: Effects on mitochondrial functionality, sirtuins, uncoupling protein 2 and antioxidant enzymes.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Jul 17;45(9):2045-2051. doi: 10.1016/j.biocel.2013.07.002.

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

[1016/j.biocel.2013.07.002](#)

AUTORES / AUTHORS: - Nadal-Serrano M; Pons DG; Sastre-Serra J; Blanquer-Rossello MD; Roca P; Oliver J

INSTITUCIÓN / INSTITUTION: - Grupo multidisciplinar de Oncología Traslacional, Institut Universitari d'Investigació en Ciències de la Salut (IUNICS), Universitat de les Illes Balears, E07122 Palma de Mallorca, Illes Balears, España.

RESUMEN / SUMMARY: - Genistein is a biologically active isoflavone with estrogenic activity and can be found in a variety of soy products. This natural compound displays a wide array of biological activities, but it is best known for

its ability to inhibit cancer progression, especially for hormone-related ones such as breast cancer. Genistein has been shown to bind both the estrogen receptor alpha (ERalpha) and the estrogen receptor beta (ERbeta), although it has a higher affinity for the ERbeta. The ERalpha/ERbeta ratio is a prognostic marker for breast tumors, and ERbeta expression could indicate the presence of tumors more benign in state, whereas ERalpha indicates malignant tumors. The objective of the present study was to investigate the effects of genistein on oxidative stress and mitochondrial functionality through its interaction with the estrogen receptor in breast cancer cell lines with different ERalpha/ERbeta ratios. The lower ERalpha/ERbeta ratio T47D cell line showed lower oxidative stress and greater mitochondrial functionality, along with an up-regulation of uncoupling protein 2 and sirtuins. On the other hand, genistein-treated MCF-7 cell line, with the highest ERalpha/ERbeta ratio, reported no changes for the control situation. On the whole, our results show different genistein effects depending on ERalpha/ERbeta ratio for oxidative stress regulation, mitochondrial functionality, and modulation of UCPs, antioxidant enzymes and sirtuins in breast cancer cell lines. Effects of genistein on oxidative stress and mitochondria could be due at least in part, to a higher ERbeta presence, but could also be due to up-regulation of ERbeta caused by the genistein treatment.

[374]

TÍTULO / TITLE: - Telomerase-specific oncolytic adenovirus: Antitumor effects on radiation-resistant head and neck squamous cell carcinoma cells.

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

REVISTA / JOURNAL: - Head Neck. 2013 Jun 1. doi: 10.1002/hed.23309.

●● Enlace al texto completo (gratis o de pago) [1002/hed.23309](#)

AUTORES / AUTHORS: - Takahashi H; Hyakusoku H; Horii C; Takahashi M; Nishimura G; Taguchi T; Kondo N; Sakakibara A; Urata Y; Sano D

INSTITUCIÓN / INSTITUTION: - Department of Otorhinolaryngology and Head and Neck Surgery, Yokohama City University School of Medicine, Yokohama, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Radioresistance remains a critical issue in the use of radiotherapy for the treatment of head and neck squamous cell carcinoma (HNSCC). This study evaluated the efficacy of combination treatment with OBP-301, a telomerase-specific replication-selective adenovirus, and radiotherapy in overcoming radioresistance by examining its effect on radiation-resistant HNSCC cells. METHODS: Radiation-resistant HNSCC cells were treated with OBP-301 and radiation in vitro and in an orthotopic nude mouse model in vivo and synergism was assessed. Apoptosis and expression of MRN complex, which plays a key role in DNA repair machinery, were also analyzed. RESULTS: Infection with OBP-301 was found to enhance the antitumor efficacy of radiation both in vitro and in vivo by inhibiting MRN complex expression and increasing apoptosis induction. CONCLUSION:

Combined OBP-301 and radiation therapy seems to overcome radioresistance in HNSCC cells by inhibiting DNA repair machinery, and may thus be a novel therapeutic strategy for treating HNSCC. © 2013 Wiley Periodicals, Inc. Head Neck, 2013.

[375]

TÍTULO / TITLE: - Exon 4 deletion variant of epidermal growth factor receptor enhances invasiveness and cisplatin resistance in epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Jul 8.

●● [Enlace al texto completo \(gratis o de pago\) 1093/carcin/bgt216](#)

AUTORES / AUTHORS: - Zhang P; Zhang P; Zhou M; Jiang H; Zhang H; Shi B; Pan X; Gao H; Sun H; Li Z

INSTITUCIÓN / INSTITUTION: - Obstetrics & Gynecology Hospital of Fudan University, Shanghai 200011, China and.

RESUMEN / SUMMARY: - Recently, de4 EGFR, a variant of epidermal growth factor receptor (EGFR) with exon 4 deletion, was identified in glioblastoma and ovarian cancer. However, its biological function on ovarian cancer is still not clear. In this study, the expression profile of de4 EGFR and its contribution to epithelial ovarian cancer cells proliferation, invasiveness and drug resistance were studied. Our results showed that 48.6% (35/72) of epithelial ovarian cancer tissues had de4 EGFR expression and the expression ratio positively correlated with clinical stages. Compared with EGFR transfectants, de4 EGFR transfectants exhibited significantly higher level of invasiveness in vitro. Mechanistically, de4 EGFR significantly upregulated the extracellular regulated protein kinase, AKT, focal adhesion kinase (FAK) and Src phosphorylation and matrix metalloproteinase-9 expression while downregulated the expression of E-cadherin. Additionally, knockdown of FAK obviously suppressed de4 EGFR-induced invasiveness. Interestingly, de4 EGFR transfectants displayed significantly lower sensitivity to cisplatin than EGFR transfectants, which could be ascribed to the upregulation of Bcl-2 and downregulation of BAD in the de4 EGFR transfectants. Collectively, these results demonstrate that de4 EGFR plays an important role in the invasiveness and cisplatin resistance in epithelial ovarian cancer cells and may provide a new potential therapeutic target for epithelial ovarian cancer.

[376]

TÍTULO / TITLE: - Fisetin inhibits growth, induces G2 /M arrest and apoptosis of human epidermoid carcinoma A431 cells: role of mitochondrial membrane potential disruption and consequent caspases activation.

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

REVISTA / JOURNAL: - Exp Dermatol. 2013 Jul;22(7):470-5. doi: 10.1111/exd.12181.

●● Enlace al texto completo (gratis o de pago) 1111/exd.12181

AUTORES / AUTHORS: - Pal HC; Sharma S; Elmets CA; Athar M; Afaq F

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL, USA.

RESUMEN / SUMMARY: - Non-melanoma skin cancers (NMSCs), one of the most common neoplasms, cause serious morbidity and mortality. Therefore, identification of non-toxic phytochemicals for prevention/treatment of NMSCs is highly desirable. Fisetin (3,3',4',7-tetrahydroxyflavone), a dietary flavonoid, present in fruits and vegetables possesses anti-oxidant and antiproliferative properties. The aim of this study was to investigate the chemotherapeutic potential of fisetin in cultured human epidermoid carcinoma A431 cells. Treatment of A431 cells with fisetin (5-80 μ m) resulted in a significant decrease in cell viability in a dose- and time-dependent manner. Employing clonogenic assay, we found that fisetin treatment significantly reduced colony formation in A431 cells. Fisetin treatment of A431 cells resulted in G2 /M arrest and induction of apoptosis. Furthermore, treatment of A431 cells with fisetin resulted in (i) decreased expression of anti-apoptotic proteins (Bcl2; Bcl-xL and Mcl-1); (ii) increased expression of pro-apoptotic proteins (Bax, Bak and Bad); (iii) disruption of mitochondrial potential; (iv) release of cytochrome c and Smac/DIABLO from mitochondria; (v) activation of caspases; and (vi) cleavage of Poly(ADP-ribose) polymerase (PARP) protein. Pretreatment of A431 cells with the pan-caspase inhibitor (Z-VAD-FMK) blocked fisetin-induced cleavage of caspases and PARP. Taken together, these data provide evidence that fisetin possesses chemotherapeutic potential against human epidermoid carcinoma A431 cells. Overall, these results suggest that fisetin could be developed as a novel therapeutic agent for the management of NMSCs.

[377]

TÍTULO / TITLE: - Prognostic value of the trichorhinophalangeal syndrome-1 (TRPS-1), a GATA family transcription factor, in early-stage breast cancer.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 May 31.

●● Enlace al texto completo (gratis o de pago) 1093/annonc/mdt190

AUTORES / AUTHORS: - Chen JQ; Bao Y; Lee J; Murray JL; Litton JK; Xiao L; Zhou R; Wu Y; Shen XY; Zhang H; Sahin AA; Katz RL; Bondy ML; Berinstein NL; Hortobagyi GN; Radvanyi LG

INSTITUCIÓN / INSTITUTION: - Departments of Breast Medical Oncology.

RESUMEN / SUMMARY: - BACKGROUND: TRPS-1 is a new GATA transcription factor that is differentially expressed in breast cancer (BC) where it been found recently to regulate epithelial-to-mesenchymal transition (EMT). PATIENTS AND METHODS: We carried out a quantitative immunohistochemistry (qIHC)

analysis of TRPS-1 expression in 341 primary-stage I-III BC samples in relation to patient clinical characteristics as well as its prognostic value, especially in an estrogen receptor-positive (ER+) subgroup. RESULTS: Higher TRPS-1 expression was significantly associated with a number of clinical and pathological characteristics as well as with improved overall survival (OS) and disease-free survival (DFS). Among stage I/II ER+ BC patients who received endocrine therapy alone, those with high TRPS-1 expression had significantly longer OS and DFS. There was also a strong association between TRPS-1 levels and the EMT marker E-cadherin in the ER+ invasive ductal carcinoma cases. Analysis of gene expression data on a panel of BC lines found that TRPS-1 expression was low or absent in BC lines having enriched mesenchymal features. CONCLUSIONS: Our data indicated that TRPS-1 is an independent prognostic marker in early-stage BC and a new EMT marker that can distinguish patients with ER+ BC who will respond longer to adjuvant endocrine therapy.

[378]

TÍTULO / TITLE: - N-acetylglucosaminyltransferase V confers hepatoma cells with resistance to anoikis through EGFR/PAK1 activation.

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

REVISTA / JOURNAL: - Glycobiology. 2013 Sep;23(9):1097-109. doi: 10.1093/glycob/cwt049. Epub 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1093/glycob/cwt049](#)

AUTORES / AUTHORS: - Liu J; Liu H; Zhang W; Wu Q; Liu W; Liu Y; Pan D; Xu J; Gu J

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology.

RESUMEN / SUMMARY: - Elevated expression and activity of N-acetylglucosaminyltransferase V (Mgat5) in hepatocellular carcinoma (HCC) is a common early event involved in tumor invasion during hepatocarcinogenesis. A better understanding of the functional role and the molecular mechanism for Mgat5-targeted protein and downstream signaling pathway behind hepatoma invasion and metastasis is urgently needed. Here, we show that Mgat5 overexpression promoted anchorage-independent growth and inhibited anoikis in hepatoma cells. This effect was reversed by glycosyltransferase inactive mutant Mgat5 L188R transfection, alpha-mannosidase II inhibitor swainsonine treatment and N-acetyl glucosamine (GlcNAc) phosphotransferase (GPT) inhibitor tunicamycin administration. Mgat5 overexpression increased p21-activated kinase 1 (PAK1) expression and shRNA-mediated PAK1 knockdown and kinase inactivation with kinase dead mutant PAK1 K299R coexpression or allosteric inhibitor P21-activated kinase inhibitor III (IPA3) treatment reversed anoikis resistance in Mgat5-overexpressed hepatoma cells. Furthermore, Mgat5 overexpression upregulated beta-1-6-GlcNAc branched N-glycosylation and following phosphorylation of epidermal growth factor receptor (EGFR) in

hepatoma cells. EGFR tyrosine kinase inhibitors AG1478 and Iressa treatment declined anchorage-independent growth and anoikis resistance, which could be rescued by constitutive active mutant PAK1 T423E coexpression in Mgat5-overexpressed hepatoma cells. Conversely, knockdown of Mgat5 reduced EGFR/PAK1-dependent anoikis resistance, which could be reversed by PAK1 T423E. These results identified Mgat5-mediated beta-1-6-GlcNAc branched N-glycosylation and following activation of EGFR as a potential novel upstream molecular event for PAK1-induced anoikis resistance in hepatoma cells, implicating that molecular targeted therapeutics against Mgat5/EGFR/PAK1 might open a new avenue for personalized medicine in advanced-stage HCC patients.

[379]

TÍTULO / TITLE: - Prognostic Gene Signatures for Hepatocellular Carcinoma: What Are We Measuring?

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jun 25.

●● [Enlace al texto completo \(gratis o de pago\) 1245/s10434-013-3071-](#)

[X](#)

AUTORES / AUTHORS: - Tanabe KK; Hoshida Y

INSTITUCIÓN / INSTITUTION: - Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA, ktanabe@partners.org.

[380]

TÍTULO / TITLE: - Cannabinoid receptor agonist as an alternative drug in 5-fluorouracil-resistant gastric cancer cells.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2541-7.

AUTORES / AUTHORS: - Xian XS; Park H; Choi MG; Park JM

INSTITUCIÓN / INSTITUTION: - Division of Gastroenterology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - Fluorouracil is the main chemotherapeutic drug used for gastrointestinal cancers, which suffers the important problem of treatment resistance. There is little information whether cannabinoid agonists can be used as an alternative drug for fluorouracil-resistant gastric cancer cells. In this study, we investigated the effects of a cannabinoid agonist, WIN-55,212-2, on 5-fluorouracil (5-FU)-resistant human gastric cancer cells, to examine whether the cannabinoid agonist may be an alternative therapy. Survival of the 5-FU-resistant gastric cancer cell line, SNU-620-5FU/1000, was not significantly reduced even by a high dose of 5-FU treatment. However, WIN-55,212-2 inhibited the proliferation of SNU-620-5FU/1000 and enhanced their apoptosis,

as indicated by an increase of apoptotic cell proportion, activated caspase-3 and Poly (ADP-ribose) polymerase cleavage. Furthermore, WIN-55,212-2 reduced phospho-extracellular-signal-regulated kinases (ERK) ½, phospho-Akt (protein kinase B), B-cell lymphoma-2 (BCL2) and BCL2-associated X (BAX) protein expression in 5-FU-resistant gastric cancer cells. These results indicate that a cannabinoid agonist may, indeed, be an alternative chemotherapeutic agent for 5-FU-resistant gastric cancer.

[381]

TÍTULO / TITLE: - Predictors of Locoregional Outcome in HER2-Overexpressing Breast Cancer Treated With Neoadjuvant Chemotherapy.

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

REVISTA / JOURNAL: - Am J Clin Oncol. 2013 Jun 24.

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

[1097/COC.0b013e31829d1eb8](#)

AUTORES / AUTHORS: - Arsenault D; Hurley J; Takita C; Reis IM; Zhao W; Rodgers S; Wright JL

INSTITUCIÓN / INSTITUTION: - Departments of *Radiation Oncology daggerMedicine, Division of Hematology and Oncology double daggerEpidemiology and Public Health and Sylvester, Division of Biostatistics parallelSurgery, Division of Surgical Oncology section signSylvester Comprehensive Cancer Center, Biostatistics and Bioinformatics Core, Miller School of Medicine, University of Miami, Miami, FL.

RESUMEN / SUMMARY: - **OBJECTIVES:** We identified prognostic factors for locoregional recurrence (LRR) in a cohort of patients with HER2-overexpressing breast cancer treated with neoadjuvant chemotherapy (NACT). **METHODS:** We reviewed records of 157 patients with HER-overexpressing tumors who received NACT between May 1999 and December 2009 and collected demographics, disease/treatment characteristics, and clinical outcome. We estimated rate of LRR by the method of cumulative incidence. **RESULTS:** Presentation was 33% stage II and 67% stage III; 29.9% were clinically node positive. All patients received NACT, 94% trastuzumab containing. 90.4% had mastectomy and 6.4% breast-conserving surgery; 3.2% had no surgery. Among surgical patients, 48% were pathologically N0, 28.8% had 1 to 3 positive nodes, and 23.7% had ≥ 4 positive nodes. 79.6% received radiation therapy (RT) to the breast/chest wall+/-supraclavicular field. Median follow-up was 43 months. Three-year cumulative incidence of LRR was 8.2%; 50% of LRR had a regional component. Predictors for LRR included use of RT (HR=4.70, P=0.006), lymph node positivity (≥ 4 vs. 0 HR=19.99, P=0.008; 1 to 3 vs. 0 HR=10.8, P=0.031), and ER status (negative vs. positive HR=6.02, P=0.006). The only risk factor for regional failure specifically was residual nodal disease (≥ 4 HR=6.5, 1 to 3 HR=5.1, P=0.031). **CONCLUSIONS:** In a cohort with stage II to III HER2-overexpressing breast cancer treated predominantly with trastuzumab-

containing NACT followed by mastectomy+/-RT, we identified omission of RT, negative ER status, and residual positive lymph nodes as significant predictors of LRR, with 50% of LRR having a regional component.

[382]

TÍTULO / TITLE: - Methanolic extract of white asparagus shoots activates TRAIL apoptotic death pathway in human cancer cells and inhibits colon carcinogenesis in a preclinical model.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Aug;43(2):394-404. doi: 10.3892/ijo.2013.1976. Epub 2013 Jun 7.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.1976](#)

AUTORES / AUTHORS: - Bousserouel S; Le Grandois J; Gosse F; Werner D; Barth SW; Marchioni E; Marescaux J; Raul F

INSTITUCIÓN / INSTITUTION: - University of Strasbourg, Unit EA 4438, Faculty of Medicine, Strasbourg, France.

RESUMEN / SUMMARY: - Shoots of white asparagus are a popular vegetable dish, known to be rich in many bioactive phytochemicals reported to possess antioxidant, and anti-inflammatory and antitumor activities. We evaluated the anticancer mechanisms of a methanolic extract of *Asparagus officinalis* L. shoots (Asp) on human colon carcinoma cells (SW480) and their derived metastatic cells (SW620), and Asp chemopreventive properties were also assessed in a model of colon carcinogenesis. SW480 and SW620 cell proliferation was inhibited by 80% after exposure to Asp (80 microg/ml). We demonstrated that Asp induced cell death through the activation of TRAIL DR4/DR5 death receptors leading to the activation of caspase-8 and caspase-3 and to cell apoptosis. By specific blocking agents of DR4/DR5 receptors we were able to prevent Asp-triggered cell death confirming the key role of DR4/DR5 receptors. We found also that Asp (80 microg/ml) was able to potentiate the effects of the cytokine TRAIL on cell death even in the TRAIL-resistant metastatic SW620 cells. Colon carcinogenesis was initiated in Wistar rats by intraperitoneal injections of azoxymethane (AOM), once a week for two weeks. One week after (post-initiation) rats received daily Asp (0.01%, 14 mg/kg body weight) in drinking water. After 7 weeks of Asp-treatment the colon of rats exhibited a 50% reduction of the number of preneoplastic lesions (aberrant crypt foci). In addition Asp induced inhibition of several pro-inflammatory mediators, in association with an increased expression of host-defense mediators. In the colonic mucosa of Asp-treated rats we also confirmed the pro-apoptotic effects observed in vitro including the activation of the TRAIL deathreceptor signaling pathway. Taken together, our data highlight the chemopreventive effects of Asp on colon carcinogenesis and its ability to promote normal cellular homeostasis.

[383]

TÍTULO / TITLE: - Inhibition of late-stage autophagy synergistically enhances pyrrolo-1,5-benzoxazepine-6-induced apoptotic cell death in human colon cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Sep;43(3):927-35. doi: 10.3892/ijo.2013.1989. Epub 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1989](#)

AUTORES / AUTHORS: - Greene LM; Nolan DP; Regan-Komito D; Campiani G; Williams DC; Zisterer DM

INSTITUCIÓN / INSTITUTION: - School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin 2, Ireland.

RESUMEN / SUMMARY: - The pyrrolo-1,5-benzoxazepines (PBOXs) are a novel group of selective apoptotic agents displaying promising therapeutic potential in both ex vivo chemotherapy-refractory patient samples and in vivo murine carcinoma models. In this report, we present novel data concerning the induction of autophagy by the PBOXs in adenocarcinoma-derived colon cancer cells. Autophagy is a lysosome-dependent degradative pathway recently associated with chemotherapy. However, whether autophagy facilitates cell survival in response to chemotherapy or contributes to chemotherapy-induced cell death is highly controversial. Autophagy was identified by enhanced expression of LC3B-II, an autophagosome marker, an increase in the formation of acridine orange-stained cells, indicative of increased vesicle formation and electron microscopic confirmation of autophagic structures. The vacuolar H⁺ ATPase inhibitor bafilomycin-A1 (BAF-A1) inhibited vesicle formation and enhanced the apoptotic potential of PBOX-6. These findings suggest a cytoprotective role of autophagy in these cells following prolonged exposure to PBOX-6. Furthermore, BAF-A1 and PBOX-6 interactions were determined to be synergistic and caspase-dependent. Potentiation of PBOX-6-induced apoptosis by BAF-A1 was associated with a decrease in the levels of the anti-apoptotic protein, Mcl-1. The data provide evidence that autophagy functions as a survival mechanism in colon cancer cells to PBOX-6-induced apoptosis and a rationale for the use of autophagy inhibitors to further enhance PBOX6induced apoptosis in colon cancer.

[384]

TÍTULO / TITLE: - CD59 is overexpressed in human lung cancer and regulates apoptosis of human lung cancer cells.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Sep;43(3):850-8. doi: 10.3892/ijo.2013.2007. Epub 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2007](#)

AUTORES / AUTHORS: - Li B; Lin H; Fan J; Lan J; Zhong Y; Yang Y; Li H; Wang Z

INSTITUCIÓN / INSTITUTION: - Renmin Hospital of Wuhan University, Wuhan 430060, P.R. China.

RESUMEN / SUMMARY: - CD59, belonging to membrane complement regulatory proteins (mCRPs), inhibits the cytolytic activity of complement and is overexpressed in many types of solid cancers. The aim of the present study was to detect the expression of CD59 in non-small cell lung cancer (NSCLC) and to investigate the relationship between decreased CD59 expression and tumorigenesis of NSCLC by transfecting recombinant retrovirus encoding shRNA targeting human CD59 into the human NSCLC cell line NCI-H157. CD59 expression in NSCLC was detected by immunocytochemistry (IHC). In the human NSCLC cell line NCI-H157, CD59 mRNA and protein expression suppressed with lentivirus-mediated RNAi was confirmed by using RT-PCR and western blotting, respectively. The proliferation and apoptosis of NCI-H157 cells was measured by using MTT assay and FACS. The resistance to complement cracking ability was detected by LDH assay. Caspase-3 expression in cells was assessed by IHC. Bcl-2 and Fas protein was determined by western blotting both in vitro and in vivo. CD59 is overexpressed in human NSCLC cancer. In NCI-H157 cells, lentivirus-mediated RNAi significantly reduced both CD59 mRNA and protein expression, which resulted in suppressing cell proliferation and increasing cell apoptosis. When incubated with fresh normal human serum (8%, v/v) for 1 h at 37 C, the cell viability was decreased and cell apoptosis was increased in siCD59-infected NCI-H157 cells compared to siCD59-C-infected cells. Reduced CD59 expression led to increased expression of caspase-3 and Fas and decreased expression of Bcl-2. Furthermore, the nude mouse tumor graft weight was significantly decreased and survival rate was significantly increased in the siCD59 group. CD59 is overexpressed in human NSCLC. CD59 silencing in NSCLC cancer cells via retrovirus-mediated RNAi can enhance complement-mediated cell apoptosis, inhibiting the growth of NSCLC. CD59 may serve as a potential target for gene therapy in NSCLC.

[385]

TÍTULO / TITLE: - Unexpected alteration of beta-catenin and c-KIT expression by 5-FU and docetaxel in p16-positive squamous cell carcinoma compared to HPV-negative HNSCC cells in vitro.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2457-65.

AUTORES / AUTHORS: - Umbreit C; Aderhold C; Faber A; Sommer JU; Sauter A; Hofheinz RD; Stern-Strater J; Hoermann K; Schultz JD

INSTITUCIÓN / INSTITUTION: - Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty of Mannheim, University of Heidelberg, Mannheim, Germany. claudia.umbreit@umm.de

RESUMEN / SUMMARY: - BACKGROUND: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common type of cancer worldwide. In several tumour entities, the tyrosine kinase receptor c-KIT is associated with tumour transformation in the epithelial tissue in cases of aberrant expression. Furthermore, tumour development and dissemination are a result of dysregulated cellular pathways such as the WNT/beta-catenin pathway. beta-Catenin is a multifunctional protein within the canonical WNT signalling pathway and a pivotal factor for the stabilization of cell-cell interactions. In malignant tissues, beta-catenin triggers tumour proliferation and progression. The aim of this study is to investigate the expression patterns of c-KIT and beta-catenin in human papillomavirus-negative and p16-positive SCC and to evaluate the chemosensitivity of the tumour cells to the chemotherapeutical agents docetaxel and 5-fluorouracil (5-FU). MATERIALS AND METHODS: We incubated the tumour cell lines with docetaxel (5 µmol/ml) and 5-FU (1 µmol/ml) and detected beta-catenin and c-KIT by immunohistochemistry and enzyme-linked immunosorbent assay (ELISA) after 48, 72, 120, 192 and 240 h. RESULTS: We found a reliable trend towards decreased beta-catenin expression levels in p16-positive and p16-negative tumour cell lines when incubated with docetaxel, in addition to induced apoptotic effect. At best, 5-FU had a slight influence on the alteration of the expression of beta-catenin. Dose escalation of docetaxel and 5-FU had no statistically significant effect on the expression of beta-catenin or c-KIT. In HPV-negative HNSCC, a reduced expression level of beta-catenin and c-KIT was detected in an incubation period-dependent manner. p16-transformed SCC (CERV196) cells were characterized by a reduced susceptibility to docetaxel induced alteration of beta-catenin expression. CONCLUSION: We were unable to confirm the clinically-substantiated increased chemosensitivity of p16-positive tumour cells in vitro. Extended studies and clinical trials are needed to investigate these findings further in HPV-associated HNSCC.

[386]

TÍTULO / TITLE: - The HDAC inhibitor, panobinostat, induces apoptosis by suppressing the expression of specificity protein 1 in oral squamous cell carcinoma.

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

REVISTA / JOURNAL: - Int J Mol Med. 2013 Jul 18. doi: 10.3892/ijmm.2013.1451.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1451](#)

AUTORES / AUTHORS: - Jeon YJ; Ko SM; Cho JH; Chae JI; Shim JH

INSTITUCIÓN / INSTITUTION: - Department of Oral Pharmacology, School of Dentistry and Institute of Dental Bioscience, BK21 project, Chonbuk National University, Jeonju 651-756, Republic of Korea.

RESUMEN / SUMMARY: - Inhibitors of histone deacetylases (HDACs) represent a novel class of therapeutic anticancer agents. Panobinostat (LBH589) induces

apoptosis through the regulation of specificity protein 1 (Sp1) in the oral squamous cell carcinoma (OSCC) cell lines, HN22 and HSC4. In this study, we analyzed the underlying signaling pathways and the mechanisms involved in this process by 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay, 4',6-diamidino-2-phenylindole (DAPI) staining, immunocytochemistry and western blot analysis. LBH589 significantly reduced cell growth and the sub-G1 cell population and induced apoptosis. Sp1 protein expression was significantly reduced following treatment with LBH589 in a concentration-dependent manner. Furthermore, LBH589 upregulated the expression of p27 and p21 and downregulated the expression of cyclin D1, myeloid cell leukemia-1 (Mcl-1) and survivin; this led to the activation of apoptotic signaling pathways through the increase of Bax expression and the decrease of Bid and Bcl-xL expression. Treatment with LBH589 also induced the cleavage of caspase3 and PARP in the HN22 and HSC4 cells. Taken together, our data demonstrate that LBH589 induces the apoptosis of OSCC cells by suppressing Sp1 expression, indicating that LBH589 may be a promising chemotherapeutic agent for the treatment of OSCC.

[387]

TÍTULO / TITLE: - Insights into the broad cellular effects of nelfinavir and the HIV protease inhibitors supporting their role in cancer treatment and prevention.

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

REVISTA / JOURNAL: - Curr Opin Oncol. 2013 Jul 18.

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

[1097/CCO.0b013e328363dfce](#)

AUTORES / AUTHORS: - Gantt S; Casper C; Ambinder RF

INSTITUCIÓN / INSTITUTION: - aDepartment of Pediatrics bDepartment of Medicine cDepartment of Epidemiology dDepartment of Global Health, University of Washington eSeattle Children's Hospital, University of Washington School of Medicine fVaccine and Infectious Disease gPublic Health Sciences hClinical Research Divisions, Fred Hutchinson Cancer Research Center, Seattle, Washington iSidney Kimmel Cancer Center at Johns Hopkins University, Baltimore, Maryland, USA.

RESUMEN / SUMMARY: - **PURPOSE OF REVIEW:** The development of HIV protease inhibitors more than two decades ago heralded a new era in HIV care, changing the infection from universally fatal to chronic but controllable. With the widespread use of protease inhibitors, there was a reduction in the incidence and mortality of HIV-associated malignancies. Studies later found these drugs to have promising direct antitumor effects. **RECENT FINDINGS:** Protease inhibitors have a wide range of effects on several cellular pathways that are important for tumorigenesis and independent of inhibition of the HIV protease, including reducing angiogenesis and cell invasion, inhibition of the Akt pathway, induction of autophagy, and promotion of apoptosis. Among protease inhibitors,

nelfinavir appears to have the most potent and broad antineoplastic activities, and also affects replication of the oncogenic herpesviruses Kaposi sarcoma-associated herpesvirus and Epstein-Barr virus. Nelfinavir is being studied for the prevention and treatment of a wide range of malignancies in persons with and without HIV infection. SUMMARY: Nelfinavir and other protease inhibitors are well tolerated, oral drugs that have promising antitumor properties, and may prove to play an important role in the prevention and treatment of several cancers. Additional insights into protease inhibitors' mechanisms of action may lead to the development of novel cancer chemotherapy agents.

[388]

TÍTULO / TITLE: - Epigenetic silencing of Bim transcription by Spi-1/PU.1 promotes apoptosis resistance in leukaemia.

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

REVISTA / JOURNAL: - Cell Death Differ. 2013 Jul 12. doi: 10.1038/cdd.2013.88.

●● [Enlace al texto completo \(gratis o de pago\) 1038/cdd.2013.88](#)

AUTORES / AUTHORS: - Ridinger-Saison M; Evanno E; Gallais I; Rimmele P; Selimoglu-Buet D; Sapharikas E; Moreau-Gachelin F; Guillouf C

INSTITUCIÓN / INSTITUTION: - [1] Institut Curie, Paris, France [2] Inserm U830, Paris, France.

RESUMEN / SUMMARY: - Deregulation of transcriptional networks contributes to haematopoietic malignancies. The transcription factor Spi-1/PU.1 is a master regulator of haematopoiesis and its alteration leads to leukaemia. Spi-1 overexpression inhibits differentiation and promotes resistance to apoptosis in erythroleukaemia. Here, we show that Spi-1 inhibits mitochondrial apoptosis in vitro and in vivo through the transcriptional repression of Bim, a proapoptotic factor. BIM interacts with MCL-1 that behaves as a major player in the survival of the preleukaemic cells. The repression of BIM expression reduces the amount of BIM-MCL-1 complexes, thus increasing the fraction of potentially active antiapoptotic MCL-1. We then demonstrate that Spi-1 represses Bim transcription by binding to the Bim promoter and by promoting the trimethylation of histone 3 on lysine 27 (H3K27me3, a repressive histone mark) on the Bim promoter. The PRC2 repressive complex of Polycomb is directly responsible for the deposit of H3K27me3 mark at the Bim promoter. SUZ12 and the histone methyltransferase EZH2, two PRC2 subunits bind to the Bim promoter at the same location than H3K27me3, distinct of the Spi-1 DNA binding site. As Spi-1 interacts with SUZ12 and EZH2, these results indicate that Spi-1 modulates the activity of PRC2 without directly recruiting the complex to the site of its activity on the chromatin. Our results identify a new mechanism whereby Spi-1 represses transcription and provide mechanistic insights on the antiapoptotic function of a transcription factor mediated by the epigenetic control of gene expression. Cell Death and Differentiation advance online publication, 12 July 2013; doi:10.1038/cdd.2013.88.

[389]

TÍTULO / TITLE: - Clinical application of the CpG island methylator phenotype to prognostic diagnosis in neuroblastomas.

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

REVISTA / JOURNAL: - J Hum Genet. 2013 Jul;58(7):428-33. doi: 10.1038/jhg.2013.64. Epub 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1038/jhg.2013.64](#)

AUTORES / AUTHORS: - Asada K; Abe M; Ushijima T

INSTITUCIÓN / INSTITUTION: - Division of Epigenomics, National Cancer Center Research Institute, Tokyo, Japan.

RESUMEN / SUMMARY: - Clinical applications of aberrant DNA methylation to cancer diagnostics and therapeutics are accelerating. Especially, the CpG island methylator phenotype (CIMP), simultaneous methylation of multiple genes, provides information that cannot be obtained by other diagnostic methods and therapeutic opportunities. CIMP is known to be associated with poor or good prognosis depending upon cancer types. We identified that CIMP in neuroblastomas (NBLs) is strongly associated with poor prognosis in Japanese NBL cases (hazard ratio (HR)=22). Almost all NBLs with MYCN amplification displayed CIMP, and even among NBLs without MYCN amplification, NBLs with CIMP had worse prognosis (HR=12). The prognostic power was faithfully reproduced in German NBL cases by the same methods, and also in Italian and Swedish NBL cases with different analytical methods. Mechanistically, methylation silencing of different sets of tumor-suppressor genes is involved in poor prognosis of NBLs with CIMP, and the presence of CIMP is most sensitively detected by methylation of the PCDHB family. For therapeutic purposes, a combination of 5-aza-2'-deoxycytidine, a DNA-demethylating drug, with 13-cis-retinoic acid, a differentiating drug, has been shown to be effective for NBLs in vitro, and further development of a better combination(s) is awaited. Now, epigenetic diagnosis and therapeutics are becoming or have become an important choice for cancer patients.

[390]

TÍTULO / TITLE: - Suppression of granzyme B activity and caspase-3 activation in leukaemia cells constitutively expressing the protease inhibitor 9.

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

REVISTA / JOURNAL: - Ann Hematol. 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1007/s00277-013-1846-](#)

[6](#)

AUTORES / AUTHORS: - Fritsch K; Finke J; Grulich C

INSTITUCIÓN / INSTITUTION: - Dpt. of Hematology and Oncology, Albert Ludwigs-University Medical Center Freiburg, Hugstetter Str. 55, 79106, Freiburg, Germany.

RESUMEN / SUMMARY: - Immune surveillance against malignant cells is mediated by cytotoxic T-lymphocytes and NK-cells (CTL/NK) that induce apoptosis through the granzyme-B-dependent pathway. The serine protease inhibitor serpinB9/protease inhibitor-9 (PI-9) is a known inhibitor of granzyme B. Ectopic expression of PI-9 in tumour cells has been reported. However, the impact of PI-9 on granzyme-B-induced apoptosis in tumour cells remains unclear. The aim of this study was to investigate the influence of constitutive PI-9 expression in leukaemia cell lines on the activity of granzyme B and apoptosis induction. PI-9 negative (lymphoblastic Jurkat cells; myeloblastic U937 cells) and PI-9-expressing cell lines (myeloblastic K562 cells, EBV-transformed LCL-1 and LCL-2 B-cells, lymphoblastic Daudi cells, AML-R cells f leukaemia and the U937 subclone U937PI-9+). For accurate granzyme B activity determination a quantitative substrate (Ac-IEPD-pNA) cleavage assay was established and caspase-3 activation measured for apoptosis assessment. Cells were treated with a cytotoxic granule isolate that has previously been shown to induce apoptosis through granzyme B signalling. We found a robust correlation between constitutive PI-9 expression levels and the suppression of granzyme B activity. Further, inhibition of granzyme B translated into reduced caspase-3 activation. We conclude, suppression of granzyme B initiated apoptosis in PI-9-expressing cells could contribute to immune evasion and the measurement of granzyme B activity with our assay might be a useful predictive marker in immune-therapeutic approaches against cancer.

[391]

TÍTULO / TITLE: - Role of autophagy in the resistance to tumour necrosis factor-related apoptosis-inducing ligand-induced apoptosis in papillary and anaplastic thyroid cancer cells.

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

REVISTA / JOURNAL: - Endocrine. 2013 Jul 3.

- Enlace al texto completo (gratis o de pago) [1007/s12020-013-9997-](#)

[8](#)

AUTORES / AUTHORS: - Jin SM; Jang HW; Sohn SY; Kim NK; Joung JY; Cho YY; Kim SW; Chung JH

INSTITUCIÓN / INSTITUTION: - Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Ilwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea.

RESUMEN / SUMMARY: - Current alternative therapies for refractory thyroid cancer such as kinase inhibitors have limitations including incomplete response and toxicity. Although tumour necrosis factor-related apoptosis-inducing ligand

(TRAIL) can induce cancer cell-specific apoptosis, various degrees of TRAIL resistance have been reported for different types of thyroid cancer cells. Here, we investigated if modulation of autophagy could improve sensitivity to TRAIL in papillary and anaplastic thyroid cancer cells. Human papillary thyroid cancer cells (TPC-1 cells) and human anaplastic thyroid cancer cells (FRO cells) were treated with TRAIL after transfection with ATG7 siRNA or control siRNA. Levels of autophagy and apoptosis were confirmed by Western blot of ATG7, LC3, caspase-3 and poly (ADP-ribose) polymerase. Viability index was determined by dimethyl-thiazole-diphenyltetrazolium bromide assay. Fraction of apoptotic cells was determined by flow cytometry. In TPC-1 cells, treatment with TRAIL increased the levels of autophagy. A low concentration (20 ng/ml) of TRAIL resulted in significantly decreased viability index and increased apoptosis. However, inhibition of autophagy with ATG7 siRNA desensitised the cells to TRAIL-induced apoptosis. In FRO cells, TRAIL did not increase the levels of autophagy. In contrast to TPC-1 cells, inhibition of autophagy with ATG7 siRNA sensitised FRO cells to TRAIL-induced apoptosis. Autophagy might contribute to the known sensitivity of papillary thyroid cancer cells to TRAIL-induced apoptosis. Inhibition of autophagy in anaplastic thyroid cancer cells could sensitise these cells to TRAIL-induced apoptosis.

[392]

TÍTULO / TITLE: - Absence of activating killer immunoglobulin-like receptor genes combined with hepatitis C viral genotype is predictive of hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Hum Immunol. 2013 Jun 10. pii: S0198-8859(13)00148-1. doi: 10.1016/j.humimm.2013.05.007.

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

[1016/j.humimm.2013.05.007](#)

AUTORES / AUTHORS: - Littera R; Zamboni F; Tondolo V; Fantola G; Chessa L; Orru N; Sanna M; Valentini D; Cappai L; Mulargia M; Caocci G; Arras M; Floris A; Orru S; La Nasa G; Carcassi C

INSTITUCIÓN / INSTITUTION: - Centro Regionale Trapianti, Ospedale R. Binaghi - ASL 8, 09126 Cagliari, Italy. Electronic address: robby.litter@gmail.com.

RESUMEN / SUMMARY: - Killer immunoglobulin-like receptors and their human leukocyte antigen class I ligands have a critical role in natural killer cell response to viral pathogens and tumors. To investigate whether killer immunoglobulin-like receptor genes could influence the chronic course of hepatitis C virus infection and/or progression to hepatocellular carcinoma we retrospectively analyzed a cohort of 228 patients transplanted for hepatitis C virus-induced cirrhotic end stage liver disease, combined or not with hepatocellular carcinoma. We found that patients completely lacking activating killer immunoglobulin-like receptor genes had a high risk of developing

hepatocellular carcinoma. Hepatitis C viral genotype and viral load are other risk factors that can influence the course of chronic hepatitis C virus infection. In our study, the risk conferred by hepatitis C viral genotypes was enhanced in patients lacking activating killer immunoglobulin-like receptors. These results point to an important role for activating killer immunoglobulin-like receptors in the control of hepatitis C virus infection and progression to hepatocellular carcinoma. In clinical practice, assessment of killer immunoglobulin-like receptor and hepatitis C viral genotype combinations should allow for more accurate monitoring of patients with chronic hepatitis C virus infection.

[393]

TÍTULO / TITLE: - Prognostic value of the Glasgow Prognostic Score in metastatic colorectal cancer in the era of anti-EGFR therapies.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):656. doi: 10.1007/s12032-013-0656-y. Epub 2013 Jul 10.

- Enlace al texto completo (gratis o de pago) [1007/s12032-013-0656-](#)

[y](#)

AUTORES / AUTHORS: - Dreanic J; Maillet M; Dhooge M; Mir O; Brezault C; Goldwasser F; Chaussade S; Coriat R

INSTITUCIÓN / INSTITUTION: - Gastro-Enterology and Digestive Oncology Unit, Cochin Teaching Hospital, AP-HP, Universite Paris Descartes, Sorbonne Paris Cite, Paris, France.

RESUMEN / SUMMARY: - The Glasgow Prognostic Score (GPS), combination of C-reactive protein and albumin, has proven its prognostic value in metastatic colorectal cancer (mCRC) patients receiving conventional cytotoxic therapy. More recently, anti-EGFR therapies have been validated in mCRC and roll forward the patients' overall survival (OS). We aimed to evaluate the prognostic accuracy of the GPS in patients receiving anti-EGFR therapy in addition to conventional chemotherapy. From January 2007 to February 2012, consecutive mCRC patients who received 5-fluorouracil-based chemotherapy plus cetuximab were included in the present analysis. Patients were eligible for the study if they met the following criteria: advanced pathologically proven MCRC, age >18 years, adequate renal function (creatinine clearance >40 ml/min), C-reactive protein and albumin and performance status evaluation before treatment initiation. A total of 49 patients received cetuximab plus 5-fluorouracil-based chemotherapy (colon, n = 34; rectum, n = 15) and were treated with a median follow-up of 35 months (16.5-74.7). Median age was 48 years old. In addition to cetuximab, patients received oxaliplatin- (n = 34, 60%) or irinotecan (n = 15, 30%)-based chemotherapy. At time of diagnosis, 55, 29 and 16% of patients had a GPS of 0 (n = 27), 1 (n = 14) and 2 (n = 8), respectively. Fifty-five, 29 and 14 % of patients add one, two or >=3 metastatic sites, respectively. Considering two groups (GPS = 0 and GPS >=1), median progression-free

survivals were significantly different ($p = 0.0084$). Median OS in the GPS 0, 1 and 2 groups were 38.2, 14 and 12.1 months, respectively ($p = 0.0093$). The results of the present study confirm that the GPS is still a simple and effective prognostic factor in the era of cetuximab therapy in mCRC patients.

[394]

TÍTULO / TITLE: - A novel bispecific EGFR/Met antibody blocks tumor-promoting phenotypic effects induced by resistance to EGFR inhibition and has potent antitumor activity.

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

REVISTA / JOURNAL: - Oncogene. 2013 Jul 1. doi: 10.1038/onc.2013.245.

●● [Enlace al texto completo \(gratis o de pago\) 1038/onc.2013.245](#)

AUTORES / AUTHORS: - Castoldi R; Ecker V; Wiehle L; Majety M; Busl-Schuller R; Asmussen M; Nopora A; Jucknischke U; Osl F; Kobold S; Scheuer W; Venturi M; Klein C; Niederfellner G; Sustmann C

INSTITUCIÓN / INSTITUTION: - Pharma Research and Early Development (pRED), Roche Diagnostics GmbH, Penzberg, Germany.

RESUMEN / SUMMARY: - Simultaneous targeting of epidermal growth factor receptor (EGFR) and Met in cancer therapy is under pre-clinical and clinical evaluation. Here, we report the finding that treatment with EGFR inhibitors of various tumor cells, when stimulated with hepatocyte growth factor (HGF) and EGF, results in transient upregulation of phosphorylated AKT. Furthermore, EGFR inhibition in this setting stimulates a pro-invasive phenotype as assessed in Matrigel-based assays. Simultaneous treatment with AKT and EGFR inhibitors abrogates this invasive growth, hence functionally linking signaling and phenotype. This observation implies that during treatment of tumors a balanced ratio of EGFR and Met inhibition is required. To address this, we designed a bispecific antibody targeting EGFR and Met, which has the advantage of a fixed 2:1 stoichiometry. This bispecific antibody inhibits proliferation in tumor cell cultures and co-cultures with fibroblasts in an additive manner compared with treatment with both single agents. In addition, cell migration assays reveal a higher potency of the bispecific antibody in comparison with the antibodies' combination at low doses. We demonstrate that the bispecific antibody inhibits invasive growth, which is specifically observed with cetuximab. Finally, the bispecific antibody potently inhibits tumor growth in a non-small cell lung cancer xenograft model bearing a strong autocrine HGF-loop. Together, our findings strongly support a combination treatment of EGFR and Met inhibitors and further evaluation of resistance mechanisms to EGFR inhibition in the context of active Met signaling. Oncogene advance online publication, 1 July 2013; doi:10.1038/onc.2013.245.

[395]

TÍTULO / TITLE: - Synergistic apoptotic effect of crocin and cisplatin on osteosarcoma cells via caspase induced apoptosis.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Jul 2;221(3):197-204. doi: 10.1016/j.toxlet.2013.06.233.

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

[1016/j.toxlet.2013.06.233](#)

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: - Crocin is well-known traditional Chinese medicine which is extracted from saffron. However, its role in osteosarcoma has not been well understood. Therefore, we used crocin and cisplatin individually or jointly on MG63 and OS732 cells so as to explore whether crocin could induce cellular apoptosis and suppress the ability of invasion of osteosarcoma cells. Cell survival rates, changes of cellular shape, cell apoptosis and cell invasion were analyzed, respectively, by 3-(4,5)-dimethylthiazolium (-z-y1)-2,5-diphenyltetrazolium bromide (MTT) assay, inverted phase contrast microscope and fluorescence microscope, flow cytometry, and Transwell invasion chamber methods. The expressions of caspase-3 and caspase-8 were detected by Western blot. The survival rate of combined application was significantly lower than that of the individual application. Apoptosis-inducing effect of combined application was much stronger than that of individual application. The invasion ability of MG63 and OS732 cells was restrained significantly in the combined group compared with the individual group and control group. Combined group has the effect of up-regulating the expressions of cleaved-caspase-3 and caspase-8. The results suggested that combination of crocin and cisplatin has a strong killing effect on osteosarcoma cells and suppresses the ability of invasion of MG63 and OS732 cells which might be related to up-regulate the expression of caspase-3 and caspase-8.

[396]

TÍTULO / TITLE: - Induction of apoptosis and the regulation of ErbB signaling by laminarin in HT-29 human colon cancer cells.

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

REVISTA / JOURNAL: - Int J Mol Med. 2013 Jun 5. doi: 10.3892/ijmm.2013.1409.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1409](#)

AUTORES / AUTHORS: - Park HK; Kim IH; Kim J; Nam TJ

INSTITUCIÓN / INSTITUTION: - Department of Food and Life Science, Pukyong National University, Nam-gu, Busan 608-737, Republic of Korea.

RESUMEN / SUMMARY: - Laminarin, found in marine brown algae, is used as a carbohydrate reserve for phytoplankton; however, it is also used in traditional Chinese medicine, and has been shown to have several biological activities,

including anticancer activities. In this study, we examined the mechanisms through which laminarin from *Laminaria digitata* induces apoptosis in HT-29 colon cancer cells, as well as the involvement of the ErbB signaling pathway. Cell viability assay revealed that laminarin induced cell death in a dose-dependent manner. Cell cycle analysis revealed that laminarin increased the percentage of cells in the sub-G1 and G2-M phase. Western blot analysis demonstrated that laminarin inhibited the heregulin-stimulated phosphorylation of ErbB2. A decrease in cellular proliferation was also observed; this was found to be dependent on ErbB, which activates c-Jun N-terminal kinase. These findings demonstrate the important role of the epidermal growth factor receptor in colon cancer tumorigenesis, and suggest the potential of laminarin as a bio-functional food with anticancer effects on human colon cancer.

[397]

TÍTULO / TITLE: - Irreversible electroporation and apoptosis in human liver cancer cells induced by nanosecond electric pulses.

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

REVISTA / JOURNAL: - Bioelectromagnetics. 2013 Jun 6. doi: 10.1002/bem.21796.

●● Enlace al texto completo (gratis o de pago) [1002/bem.21796](#)

AUTORES / AUTHORS: - Xiao D; Yao C; Liu H; Li C; Cheng J; Guo F; Tang L

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Biorheological Science and Technology, Ministry of Education, College of Bioengineering, Chongqing University, Chongqing, China.

RESUMEN / SUMMARY: - The goal of this study was to assess the effect of nanosecond electric pulses on HepG2 human liver cancer cells. Electric pulses with a high strength of 10 kV/cm, duration of 500 ns and frequency of 1 Hz were applied to the cells. After delivery of electric pulses, apoptosis, intracellular calcium ion concentrations, transmembrane mitochondrial potentials, electropermeabilization and recovery from electropermeabilization in cells were investigated. The results showed that electric pulse treatment for 20 s and more could trigger apoptosis in cells. Real-time observation indicated an immediate increase in intracellular calcium ion concentration and a dramatic decrease in mitochondrial membrane potential in cells responding to electric pulses. In subsequent experiments, propidium iodide uptake in cells emerged after exposure to electric pulses, indicating electropermeabilization of the cell membrane. Furthermore, recovery from electropermeabilization was not observed even 4 h after the stimulation, demonstrating that irreversible electropermeabilization was induced by electric pulses. In conclusion, electric pulses with a high strength and nanosecond duration can damage cancer cells, accompanied by a series of intracellular changes, providing strong evidence for the application of electric pulses in cancer treatment. Bioelectromagnetics. © 2013 Wiley Periodicals, Inc.

[398]

TÍTULO / TITLE: - Inhibition of Wnt signaling induces cell apoptosis and suppresses cell proliferation in cholangiocarcinoma cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 21. doi: 10.3892/or.2013.2560.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2560](#)

AUTORES / AUTHORS: - Zhang KS; Zhou Q; Wang YF; Liang LJ

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary Surgery, The First Affiliated Hospital of Sun YatSen University, Guangzhou, Guangdong 510080, P.R. China.

RESUMEN / SUMMARY: - The aim of the present study was to explore possible gene therapy for hilar cholangiocarcinoma by detecting the activation of the Wnt signaling pathway in 4 cholangiocarcinoma cell lines and inhibiting its expression by RNA interference (RNAi) targeting key factors of this pathway. The expression levels of the Wnt pathway-related factors, Wnt2, Wnt3, beta-catenin and transcription factor 4, and its target genes, c-myc and cyclin D1, in 4 cholangiocarcinoma cell lines were detected by RT-PCR, western blotting and immunofluorescence microscopy. After transfection of siRNAs targeting Wnt2 and beta-catenin into FRH0201 cells, the expression of the Wnt pathway-related factors and its target genes was again detected, and the cell cycle distribution, apoptosis and proliferation were analyzed by flow cytometry and MTT assay. Activation of the Wnt pathway and the expression of its target genes were detected in all 4 cell lines at various levels. After siRNA transfection, the expression of the target genes in the FRH0201 cells was significantly downregulated. In addition, the Wnt pathway was blocked, cell apoptosis was enhanced and cell proliferation was suppressed. In conclusion, the Wnt signaling pathway is activated in cholangiocarcinoma cells. RNAi technology targeting Wnt2 and beta-catenin may be a possible gene therapy for hilar cholangiocarcinoma.

[399]

TÍTULO / TITLE: - Cordycepin increases sensitivity of Hep3B human hepatocellular carcinoma cells to TRAIL-mediated apoptosis by inactivating the JNK signaling pathway.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 4. doi: 10.3892/or.2013.2589.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2589](#)

AUTORES / AUTHORS: - Lee HH; Jeong JW; Lee JH; Kim GY; Cheong J; Jeong YK; Yoo YH; Choi YH

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology and Medi-Farm Industrialization Research Center, Dong-A University, Busan 604714, Republic of Korea.

RESUMEN / SUMMARY: - Resistance to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis has been reported in various cancer cells. Cordycepin, a specific polyadenylation inhibitor, is the main functional component in *Cordyceps militaris*, which possesses many pharmacological activities including antitumor and anti-inflammation. In the present study, we demonstrated that treatment of cordycepin sensitized TRAIL-resistant Hep3B human hepatocellular carcinoma cells to TRAIL-mediated apoptosis as evidenced by formation of apoptotic bodies, chromatin condensation and accumulation of cells in the sub-G1 phase. The induction of apoptosis following co-treatment with cordycepin and TRAIL in Hep3B cells appeared to be correlated with modulation of Bcl-2 family protein expression and activation of the caspase cascade, which resulted in the cleavage of poly(ADP-ribose) polymerase and beta-catenin. In addition, cordycepin treatment also inhibited activation of c-Jun N-terminal kinase (JNK). Pretreatment with SP600125, a JNK inhibitor, resulted in a significantly increased sub-G1 population and caspase activity in cordycepin plus TRAIL-mediated apoptosis. Taken together, these results indicate that JNK acts as a key regulator of apoptosis in response to combined treatment with cordycepin and TRAIL in human hepatocellular carcinoma Hep3B cells.

[400]

TÍTULO / TITLE: - Replacement of a Quinone by a 5-O-Acetylhydroquinone Abolishes the Accidental Necrosis Inducing Effect while Preserving the Apoptosis-Inducing Effect of Renieramycin M on Lung Cancer Cells.

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

REVISTA / JOURNAL: - J Nat Prod. 2013 Jul 22.

●● Enlace al texto completo (gratis o de pago) [1021/np400277m](#)

AUTORES / AUTHORS: - Cheun-Arom T; Chanvorachote P; Sirimangkalakitti N; Chuanasa T; Saito N; Abe I; Suwanborirux K

INSTITUCIÓN / INSTITUTION: - Center of Bioactive Natural Products from Marine Organisms and Endophytic Fungi, Department of Pharmacognosy and Pharmaceutical Botany, Chulalongkorn University, Bangkok 10330, Thailand.

RESUMEN / SUMMARY: - Renieramycin M (1), a bistetrahydroisoquinolinequinone alkaloid isolated from the marine sponge *Xestospongia* sp., has been reported to possess promising anticancer effects. However, its accidental necrosis inducing effect has limited further development due to concerns of unwanted toxicity. The presence of two quinone moieties in its structure was demonstrated to induce accidental necrosis and increase reactive oxygen species (ROS) levels. Therefore, one quinone of 1 was modified to produce the 5-O-acetylated hydroquinone derivative (2), and 2 dramatically reduced the

accidental necrosis inducing effect while preserving the apoptosis-inducing effect of parent 1 on lung cancer H23 cells. Addition of the antioxidant N-acetylcysteine suppressed the accidental necrosis mediated by 1, suggesting that its accidental necrosis inducing effect was ROS-dependent. The fluorescent probe dihydroethidium revealed that the accidental necrosis mediated by 1 was due to its ability to generate intracellular superoxide anions. Interestingly, the remaining quinone in 2 was required for its cytotoxicity, as the 5,8,15,18-O-tetraacetylated bishydroquinone derivative (3) exhibited weak cytotoxicity compared to 1 and 2. The present study demonstrates a simple way to eliminate the undesired accidental necrosis inducing effect of substances that may be developed as improved anticancer drug candidates.

[401]

TÍTULO / TITLE: - Polyethylene glycated leukemia inhibitory factor antagonist inhibits human blastocyst implantation and triggers apoptosis by down-regulating embryonic AKT.

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

REVISTA / JOURNAL: - Fertil Steril. 2013 Jul 19. pii: S0015-0282(13)00723-1. doi: 10.1016/j.fertnstert.2013.06.023.

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

1016/j.fertnstert.2013.06.023

AUTORES / AUTHORS: - Lalitkumar S; Boggavarapu NR; Menezes J; Dimitriadis E; Zhang JG; Nicola NA; Gemzell-Danielsson K; Lalitkumar LP

INSTITUCIÓN / INSTITUTION: - Department of Women's and Children's Health, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

RESUMEN / SUMMARY: - **OBJECTIVE:** To study the effect of polyethylene glycated leukemia inhibitory factor (LIF) antagonist (PEGLA) in the human blastocyst viability and implantation process. **DESIGN:** In vitro study. **SETTING:** University hospital and research laboratory. **PATIENT(S):** Endometrial biopsy samples from fertile donors (n = 20), and surplus, frozen, good-quality human embryos obtained from an in vitro fertilization (IVF) clinic that survived thawing (n = 51). **INTERVENTION(S):** Timed human endometrial biopsy on the day of luteinizing hormone peak + 4 days (LH + 4). **MAIN OUTCOME MEASURE(S):** Human embryo attachment rate, embryo quality, and expression of AKT and caspase-3. **RESULT(S):** PEGLA significantly reduced the embryo attachment rate to the endometrial construct. It decreased both mRNA and protein for LIF in the endometrial construct. Inhibition of embryonic LIF triggered apoptosis. Analysis of these blastocysts by immunofluorescence and real-time polymerase chain reaction showed a down-regulation in AKT activation and an increase in caspase-3 activation compared with the control group of blastocysts. **CONCLUSION(S):** The LIF inhibitor PEGLA could be a potential nonsteroidal fertility-regulating agent in humans. It acts on endometrial epithelial cells by down-regulating endometrial epithelial LIF. Inhibition of blastocyst LIF

decreased its cell survival factor p-AKT and increased apoptosis (cleaved caspase-3). This highlights that embryonic LIF is vital for human embryo implantation.

[402]

TÍTULO / TITLE: - Viability inhibition effect of gambogic acid combined with cisplatin on osteosarcoma cells via mitochondria-independent apoptotic pathway.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1740-](#)

[5](#)

AUTORES / AUTHORS: - Zhao W; You CC; Zhuang JP; Zu JN; Chi ZY; Xu GP; Yan JL

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, The First Affiliated Hospital of Harbin Medical University, 23 Youzheng Street, Harbin, 150001, China.

RESUMEN / SUMMARY: - We previously demonstrated that gambogic acid (GA) is a promising chemotherapeutic compound for human osteosarcoma treatment. The aim of this study was to detect whether the combination of lower-dose GA (0.3 mg/L) and cisplatin (CDDP) (1 mg/L) could perform a synergistic effect on inhibiting tumor in four osteosarcoma cell lines. Our results showed that the combination between GA at lower dose and CDDP significantly exerts a synergistic effect on inhibiting the cellular viability in MG63, HOS, and U2OS cells. In contrast, an antagonistic character was detected in SAOS2 cells exposed to the combined use of lower-dose GA (0.3 mg/L) and CDDP (1 mg/L). Then, analysis of cell cycle showed the combination of both drugs significantly induced the G2/M phase arrest, without any difference relative to GA treatment alone, in MG63 cells. Flow-cytometric analysis of cell apoptosis displayed that the apoptotic rate in the combination group is higher than that in GA treatment alone in MG63, HOS, and U2OS cells. The combined use of both drugs had no effect on mitochondrial membrane potential, but promoted the apoptosis-inducing function through triggering of CDDP in the three cell lines. By measurement of mitochondrial membrane potential, the activity of caspase-3 and the expressions of caspase-8 and caspase-9, it was showed that the apoptosis-promoting effect of the combined use of both drugs could be dependent on the death receptor apoptosis pathway, not dependent on the mitochondria apoptosis mechanism. This research, for the first time, demonstrates that GA could increase the chemotherapeutic effect of CDDP in human osteosarcoma treatment through inducing the cell cycle arrest and promoting cell apoptosis.

[403]

TÍTULO / TITLE: - MK-2206 induces cell cycle arrest and apoptosis in HepG2 cells and sensitizes TRAIL-mediated cell death.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Jun 25.

- Enlace al texto completo (gratis o de pago) [1007/s11010-013-1737-0](#)

[0](#)

AUTORES / AUTHORS: - Jiao P; Zhou YS; Yang JX; Zhao YL; Liu QQ; Yuan C; Wang FZ

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Atherosclerosis in Universities of Shandong, Taishan Medical University, Taian, 271016, People's Republic of China.

RESUMEN / SUMMARY: - It has become evident that AKT inhibitors have great potential in cancer treatment. In this study, we investigate the anticancer activity of MK-2206, a novel AKT inhibitor, on HepG2 hepatocellular carcinoma cell, and to show whether MK-2206 enhances the apoptosis-inducing potential of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The cell growth inhibition was evaluated by MTT assay and colony formation assay. Cell cycle distribution was assessed by propidium iodide flow cytometry. Apoptosis was determined by AnnexinV-FITC/PI double staining assay and caspase-9, caspase-7, caspase-3, and PARP cleavage. The results of present study showed that MK-2206-induced G1-phase arrest was associated with a marked decrease in the protein expression of cyclin D1 with concomitant induction of p21 and p27. MK-2206-induced apoptosis was characterized by cleavage of a pro-caspase in a concentration-dependent manner. Moreover, the MAP family kinases p38 kinase and JNK were activated by exposure to MK-2206. SB203580, an p38-specific inhibitor, partially blocked MK-2206-induced death of HepG2 cells and caspase activation. A combination of MK-2206 with TRAIL significantly inhibited growth of TRAIL resistant HepG2 cells. Taken together, our findings provide a new insight to better understand anticancer mechanisms of MK-2206, at least in HepG2 cell. Using of MK-2206 as a potent sensitizer to TRAIL-induced apoptotic cell death offers a promising means of enhancing the efficacy of TRAIL-based HCC treatments.

[404]

TÍTULO / TITLE: - Dioscin, a natural steroid saponin, induces apoptosis and DNA damage through reactive oxygen species: A potential new drug for treatment of glioblastoma multiforme.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Jul 16;59C:657-669. doi: 10.1016/j.fct.2013.07.012.

- Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.07.012](#)

AUTORES / AUTHORS: - Lv L; Zheng L; Dong D; Xu L; Yin L; Xu Y; Qi Y; Han X; Peng J

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Dalian Medical University, 9 Western Lvshun South Road, Dalian 116044, China.

RESUMEN / SUMMARY: - Dioscin, a natural product obtained from medicinal plants shows lipid-lowering, anti-cancer and hepatoprotective effects. However, the effect of it on glioblastoma is unclear. In this study, dioscin significantly inhibited proliferation of C6 glioma cells and caused reactive oxygen species (ROS) generation and Ca²⁺ release. ROS accumulation affected levels of malondialdehyde, nitric oxide, glutathione disulfide and glutathione, and caused cell apoptosis. In addition, ROS generation caused mitochondrial damage including structural changes, increased mitochondrial permeability transition and decreased mitochondria membrane potential, which led to the release of cytochrome C, nuclear translocation of programmed cell death-5 and increased activities of caspase-3,9. Simultaneously, dioscin down-regulated protein expression of Bcl-2, Bcl-xl, up-regulated expression of Bak, Bax, Bid and cleaved poly (ADP-ribose) polymerase. Also, oxygen stress induced S-phase arrest of cancer cells by way of regulating expression of DNA Topo I, p53, CDK2 and Cyclin A and caused DNA damage. In a rat allograft model, dioscin significantly inhibited tumor size and extended the life cycle of the rats. In conclusion, dioscin shows noteworthy anti-cancer activity on glioblastoma cells by promoting ROS accumulation, inducing DNA damage and activating mitochondrial signal pathways. Ultimately, we believe dioscin has promise as a new therapy for the treatment of glioblastoma.

[405]

TÍTULO / TITLE: - Epigenetic downregulation of RUNX3 by DNA methylation induces docetaxel chemoresistance in human lung adenocarcinoma cells by activation of the AKT pathway.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Jul 24. pii: S1357-2725(13)00236-7. doi: 10.1016/j.biocel.2013.07.013.

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

[1016/j.biocel.2013.07.013](#)

AUTORES / AUTHORS: - Zheng Y; Wang R; Song HZ; Pan BZ; Zhang YW; Chen LB

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Jinling Hospital, Clinical School of Nanjing, Second Military Medical University, 305 Zhongshan East Road, Nanjing 210002, PR China.

RESUMEN / SUMMARY: - The RUNX3 gene has been shown to function as a tumor suppressor gene implicated in various cancers, but its association with tumor chemoresistance has not been fully understood. Here, we investigated the effect of epigenetic downregulation of RUNX3 in docetaxel resistance of

human lung adenocarcinoma and its possible molecular mechanisms. RUNX3 was found to be downregulated by hypermethylation in docetaxel-resistant lung adenocarcinoma cells. Its overexpression could resensitize cells to docetaxel both in vitro and in vivo by growth inhibition, enhancement of apoptosis and G1 phase arrest. Conversely, knockdown of RUNX3 could lead to the decreased sensitivity of parental human lung adenocarcinoma cells to docetaxel by enhancing proliferative capacity. Furthermore, we showed that overexpression of RUNX3 could inactivate the AKT/GSK3beta/beta-catenin signaling pathway in the docetaxel-resistant cells. Importantly, co-transfection of RUNX3 and constitutively active Akt1 could reverse the effects of RUNX3 overexpression, while treatment with the MK-2206 (AKT inhibitor) mimicked the effects of RUNX3 overexpression in docetaxel-resistant human lung adenocarcinoma cells. Immunohistochemical analysis revealed that decreased RUNX3 expression was correlated with high expression of Akt1 and decreased sensitivity of patients to docetaxel-based chemotherapy. Taken together, our results suggest that epigenetic downregulation of RUNX3 can induce docetaxel resistance in human lung adenocarcinoma cells by activating AKT signaling and increasing expression of RUNX3 may represent a promising strategy for reversing docetaxel resistance in the future.

[406]

TÍTULO / TITLE: - Cytochalasin B induces apoptosis through the mitochondrial apoptotic pathway in HeLa human cervical carcinoma cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 17. doi: 10.3892/or.2013.2617.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2617](#)

AUTORES / AUTHORS: - Hwang J; Yi M; Zhang X; Xu Y; Jung JH; Kim DK

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Chemistry and Institute of Basic Science, Inje University, Gimhae, South Gyeongsang 621749, Republic of Korea.

RESUMEN / SUMMARY: - Cytochalasin B (CB) is a cell-permeable mycotoxin. It inhibits cytoplasmic division by blocking the formation of contractile microfilaments, it inhibits cell movement and induces nuclear extrusion. In the present study, we investigated the anticancer activity of CB in HeLa human cervical carcinoma cells. CB showed significant cytotoxicity, with an IC₅₀ of 7.9 microM, in a WST-8 assay and significantly inhibited cell proliferation. Furthermore, results from Annexin V-FITC/propidium iodide double-staining indicated that CB induced early apoptosis of HeLa cells in a time-dependent manner. The cells exhibited apoptotic morphology, including cell shrinkage and nuclear condensation. CB induced cell cycle arrest at the S phase. We also observed inhibition of DNA replication in a [³H]-thymidine incorporation assay. Furthermore, CB induced a time-dependent increase in reactive oxygen species and a decrease in mitochondrial membrane potential. Western blot analysis

showed an increase in levels of mitochondrial factors Bax and Bcl-2, which was followed by activation of caspase-9 and -3. These results suggested that CB induced apoptosis via a mitochondrial-dependent pathway in HeLa cells.

[407]

TÍTULO / TITLE: - Utility of progranulin and serum leukocyte protease inhibitor as diagnostic and prognostic biomarkers in ovarian cancer.

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

REVISTA / JOURNAL: - Cancer Epidemiol Biomarkers Prev. 2013 Jul 22.

●● Enlace al texto completo (gratis o de pago) [1158/1055-9965.EPI-12-1368](#)

AUTORES / AUTHORS: - Carlson AM; Maurer MJ; Goergen KM; Kalli KR; Erskine CL; Behrens MD; Knutson KL; Block MS

INSTITUCIÓN / INSTITUTION: - Mayo Medical School, Mayo Clinic.

RESUMEN / SUMMARY: - Background: Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death in females and leading gynecologic cause of cancer death. Despite the identification of multiple serum biomarkers, methods to identify early stage disease and predict prognosis remain scarce. We have evaluated two biologically connected biomarkers, serum leukocyte protease inhibitor (SLPI) and progranulin (PGRN). Methods: 200 frozen plasma samples were acquired from the Mayo Clinic Biospecimen Repository for Ovarian Cancer Research. Samples were obtained from 50 patients with benign conditions, 50 with AJCC stage I and II EOC, and 100 with AJCC stage III and IV EOC patients. Samples were obtained prior to surgical resection of a mass and were analyzed for levels of SLPI and PGRN using enzyme-linked immunosorbent assays. Receiver-operator characteristic curves were generated. Median follow-up was 48 months. Results: Absolute levels of SLPI were elevated in patients with EOC compared to benign disease and predicted the presence of EOC (AUC of 0.812. P = 0.04); SLPI remained elevated in the subset of patients with normal CA-125. PGRN levels were not significantly increased in early stage or late stage EOC patients as a whole, but higher PGRN was associated with decreased overall survival. Conclusions: SLPI levels are elevated in epithelial ovarian cancer, and SLPI shows promise as a diagnostic biomarker for patients with both elevated and normal CA-125 levels. Higher PGRN is associated with decreased overall survival. Impact: SLPI is elevated in EOC and warrants investigation in a screening study in women at risk for EOC.

[408]

TÍTULO / TITLE: - mTOR kinase inhibitors as potential cancer therapeutic drugs.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jun 20. pii: S0304-3835(13)00467-9. doi: 10.1016/j.canlet.2013.06.017.

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

1016/j.canlet.2013.06.017

AUTORES / AUTHORS: - Sun SY

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA, USA. Electronic address: ssun@emory.edu.

RESUMEN / SUMMARY: - The mammalian target of rapamycin (mTOR) plays a critical role in the positive regulation of cell growth and survival primarily through direct interaction with raptor (forming mTORC complex 1; mTORC1) or rictor (forming mTOR complex 2; mTORC2). The mTOR axis is often activated in many types of cancer and thus has become an attractive cancer therapeutic target. The modest clinical anticancer activity of conventional mTOR allosteric inhibitors, rapamycin and its analogs (rapalogs), which preferentially inhibit mTORC1, in most types of cancer, has encouraged great efforts to develop mTOR kinase inhibitors (TORKinibs) that inhibit both mTORC1 and mTORC2, in the hope of developing a novel generation of mTOR inhibitors with better therapeutic efficacy than rapalogs. Several TORKinibs have been developed and actively studied pre-clinically and clinically. This review will highlight recent advances in the development and research of TORKinibs and discuss some potential issues or challenges in this area.

[409]

TÍTULO / TITLE: - 99mTc-Labeled Small-Molecule Inhibitors of Prostate-Specific Membrane Antigen for Molecular Imaging of Prostate Cancer.

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

REVISTA / JOURNAL: - J Nucl Med. 2013 Aug;54(8):1369-76. doi: 10.2967/jnumed.112.116624. Epub 2013 Jun 3.

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

2967/jnumed.112.116624

AUTORES / AUTHORS: - Hillier SM; Maresca KP; Lu G; Merkin RD; Marquis JC; Zimmerman CN; Eckelman WC; Joyal JL; Babich JW

INSTITUCIÓN / INSTITUTION: - Molecular Insight Pharmaceuticals, Cambridge, Massachusetts.

RESUMEN / SUMMARY: - Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancer, and small-molecule radiopharmaceuticals targeting PSMA rapidly detect the location and extent of disease. Here we evaluated preclinically 4 novel (99m)Tc-labeled small-molecule inhibitors of PSMA with the potential for clinical translation for molecular imaging of prostate cancer in humans. METHODS: Four PSMA inhibitors derived from the glutamate-urea-glutamate or glutamate-urea-lysine pharmacophores conjugated to CIM or TIM chelators were radiolabeled with (99m)Tc and

evaluated in vitro and in vivo. RESULTS: High-affinity, saturable binding to PSMA on LNCaP cells was observed with Kd values of 0.64 +/- 0.46 nM for (99m)Tc-MIP-1427, 1.07 +/- 0.89 nM for (99m)Tc-MIP-1404, 1.75 +/- 0.32 nM for (99m)Tc-MIP-1428, and 4.35 +/- 0.35 nM for (99m)Tc-MIP-1405. (99m)Tc-labeled PSMA inhibitors did not bind human prostate cancer PC3 cells, which lack PSMA, demonstrating specificity, and binding was abolished with 2-(phosphonomethyl)pentanedioic acid (PMPA), a structurally unrelated PSMA inhibitor. (99m)Tc-labeled PSMA inhibitors were shown to internalize at 37 degrees C. Uptake in LNCaP xenografts ranged from 9.3% to 12.4% injected dose per gram at 1 h after injection and from 7.2% to 11.0% at 4 h, with tumor-to-blood ratios ranging from 29:1 to 550:1 and tumor-to-skeletal muscle ratios ranging from 31:1 to 157:1 at 4 h. (99m)Tc-MIP-1404 exhibited the best combination of high tumor uptake and rapid clearance from kidney and nontarget tissues. (99m)Tc-MIP-1404 specifically bound to PSMA in vivo as demonstrated by the absence of uptake in PC3 xenografts and by competition with PMPA. SPECT/CT imaging corroborated the tissue distribution results, demonstrating uptake only in PSMA-expressing kidney and tumor tissue and clearance through the urinary bladder. CONCLUSION: These (99m)Tc-labeled radiopharmaceuticals targeting PSMA may provide a SPECT molecular imaging option to assist in the initial diagnosis of prostate cancer and the management of patient care by monitoring disease progression.

[410]

TÍTULO / TITLE: - Antitumor Activity of 2-Hydroxycinnamaldehyde for Human Colon Cancer Cells through Suppression of beta-Catenin Signaling.

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

REVISTA / JOURNAL: - J Nat Prod. 2013 Jul 26;76(7):1278-84. doi: 10.1021/np400216m. Epub 2013 Jul 15.

●● Enlace al texto completo (gratis o de pago) [1021/np400216m](#)

AUTORES / AUTHORS: - Lee MA; Park HJ; Chung HJ; Kim WK; Lee SK

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, Natural Products Research Institute, Seoul National University, Seoul 151-742, Korea.

RESUMEN / SUMMARY: - The antiproliferative and antitumor activities of 2-hydroxycinnamaldehyde (1), a phenylpropanoid isolated from the bark of Cinnamomum cassia, were investigated using human colorectal cancer cells. Compound 1 exhibited antiproliferative effects in HCT116 colon cancer cells, accompanied by modulation of the Wnt/beta-catenin cell signaling pathway. This substance was found also to inhibit beta-catenin/T-cell factor (TCF) transcriptional activity in HEK293 cells and HCT116 colon cancer cells. Further mechanistic investigations in human colon cancer cells with aberrantly activated Wnt/beta-catenin signaling showed that 1 significantly suppressed the binding of beta-catenin/TCF complexes to their specific genomic targets in the nucleus and led to the down-regulation of Wnt target genes such as c-myc and cyclin

D1. In an in vivo xenograft model, the intraperitoneal administration of 1 (10 or 20 mg/kg body weight, three times/week) for four weeks suppressed tumor growth in athymic nude mice implanted with HCT116 colon cancer cells significantly, without any apparent toxicity. In an ex vivo biochemical analysis of the tumors, compound 1 was also found to suppress Wnt target genes associated with tumor growth including beta-catenin, c-myc, cyclin D1, and survivin. The suppression of the Wnt/beta-catenin signaling pathway is a plausible mechanism of action underlying the antiproliferative and antitumor activity of 1 in human colorectal cancer cells.

[411]

TÍTULO / TITLE: - Association of cytotoxic T-lymphocyte antigen 4 genetic polymorphism, hepatitis C viral infection and B-cell non-Hodgkin lymphoma: an Egyptian study.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Aug 6.

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

[3109/10428194.2013.820294](https://doi.org/10.3109/10428194.2013.820294)

AUTORES / AUTHORS: - Khorshied MM; Gouda HM; Khorshid OM

INSTITUCIÓN / INSTITUTION: - Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University , Cairo , Egypt.

RESUMEN / SUMMARY: - Genetic and environmental factors are involved in the pathogenesis of non-Hodgkin lymphoma (NHL). The present study aimed to investigate the association between cytotoxic T-lymphocyte antigen 4 (CTLA-4) genetic polymorphism, hepatitis C virus (HCV) infection and B-cell NHL risk in Egypt. Genotyping of CTLA-4 single nucleotide polymorphisms (SNPs) was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay for 181 adult patients with B-NHL and 200 controls. Our study revealed that CTLA-4 + 49 A/G polymorphism conferred increased risk of B-NHL (odds ratio [OR] = 1.7, 95% confidence interval [CI] = 1.36-2.565). The prevalence of HCV infection in individuals harboring the mutant genotype + 49 A/G and - 318 C/T SNPs was higher in patients with B-NHL and was associated with increased risk of B-NHL (OR = 2.79, 95% CI = 1.24-6.93 for + 49 A/G and OR = 3.9, 95% CI = 1.01-15.98 for - 318 C/T). In conclusion, some SNPs of CTLA-4 are genetic risk factors for B-NHL. Moreover, this study identified an association of CTLA-4 + 49 A/G and - 318 C/T promoter polymorphisms with HCV infection.

[412]

TÍTULO / TITLE: - S100A2 is a predictive biomarker of adjuvant therapy benefit in pancreatic adenocarcinoma.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Aug;49(12):2643-2653. doi: 10.1016/j.ejca.2013.04.017. Epub 2013 May 28.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejca.2013.04.017

AUTORES / AUTHORS: - Bachet JB; Marechal R; Demetter P; Bonnetain F; Cros J; Svrcek M; Bardier-Dupas A; Hammel P; Sauvanet A; Louvet C; Paye F; Vaillant JC; Andre T; Closset J; Salmon I; Emile JF; Van Laethem JL

INSTITUCIÓN / INSTITUTION: - Medical University Pierre et Marie Curie, UFR Paris VI, 91-105 Boulevard de l'Hopital, 75634 Paris, France; EA4340 "Epidemiologie et oncogenese des tumeurs digestives", Faculte de medecine PIFO, UVSQ, 9 Boulevard d'Alembert, 78280 Guyancourt, France; Department of Hepatogastroenterology, Pitie Salpetriere Hospital, APHP, 47-83 Boulevard de l'hopital, 75651 Paris Cedex 13, France; Department of Gastroenterology and Gastrointestinal Cancer Unit, Erasme Hospital, ULB, 808 Route de Lennik, 1070 Bruxelles, Belgium. Electronic address: jean-baptiste.bachet@psl.aphp.fr.

RESUMEN / SUMMARY: - BACKGROUND: Prognosis of patients with pancreatic adenocarcinoma (PAC) remains poor. S100A2 has been recently suggested as a negative prognostic biomarker in PAC. We aimed to investigate its prognostic and/or predictive value in a large independent multicentric cohort of patients with resected PAC. METHODS: Sequential samples of 471 patients were retrospectively collected; 142 patients did not receive adjuvant treatment (30%) and 329 (70%) received an adjuvant treatment. We measured protein levels of S100A2 by semiquantitative immunohistochemistry with tissue microarrays and correlated with patients' overall survival (OS) and disease-free survival (DFS). RESULTS: S100A2 protein status was obtained in 462 (98%) patients. Its expression was low, moderate or high in 59%, 12% and 2% of cases, respectively. It was not correlated with DFS or OS in the whole population, neither in the subgroup of patients who did not receive adjuvant treatment. However among patients who received an adjuvant therapy, moderate/high levels of S100A2 were significantly associated with longer OS and DFS in multivariate analysis (hazard ratios of 0.63, p=0.022 and 0.67, p=0.017, respectively), whereas low S100A2 was not. Interaction tests for adjuvant therapy were statistically significant both for the OS and the DFS (p=0.001 and p=0.023, respectively). On multivariate analysis, S100A2 retained independent predictive values (OS: p<0.001, DFS: p=0.003) with a significant benefit of adjuvant therapy for those patients with moderate/high S100A2. CONCLUSIONS: S100A2 expression predicts longer DFS and OS in patients treated with adjuvant therapy and should be evaluated as a predictive biomarker.

[413]

TÍTULO / TITLE: - Aldose reductase inhibition enhances TRAIL-induced human colon cancer cell apoptosis through AKT/FOXO3a-dependent upregulation of death receptors.

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

REVISTA / JOURNAL: - Free Radic Biol Med. 2013 Oct;63:280-90. doi: 10.1016/j.freeradbiomed.2013.05.039. Epub 2013 May 31.

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

[1016/j.freeradbiomed.2013.05.039](#)

AUTORES / AUTHORS: - Shoeb M; Ramana KV; Srivastava SK

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, TX 77555, USA.

RESUMEN / SUMMARY: - One of the major problems associated with the chemotherapy of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) that selectively kills tumor cells is decreased drug resistance. This warranted the development of safe novel pharmacological agents that could sensitize the tumor cells to TRAIL. Herein, we examined the role of aldose reductase (AR) in sensitizing cancer cells to TRAIL and potentiating TRAIL-induced apoptosis of human colon cancer cells. We demonstrate that AR inhibition potentiates TRAIL-induced cytotoxicity in cancer cells by upregulation of both death receptor (DR)-5 and DR4. Knockdown of DR5 and DR4 significantly (>85%) reduced the sensitizing effect of the AR inhibitor fidarestat on TRAIL-induced apoptosis. Further, AR inhibition also downregulates cell survival proteins (Bcl-xL, Bcl-2, survivin, XIAP, and FLIP) and upregulates the expression of proapoptotic proteins such as Bax and alters mitochondrial membrane potential, leading to cytochrome c release, caspases-3 activation, and PARP cleavage. We found that AR inhibition regulates AKT/PI3K-dependent activation of forkhead transcription factor FOXO3a. Knockdown of FOXO3a significantly (>80%) abolished AR inhibition-induced upregulation of DR5 and DR4 and apoptosis in colon cancer cells. Overall, our results show that fidarestat potentiates TRAIL-induced apoptosis through downregulation of cell survival proteins and upregulation of death receptors via activation of the AKT/FOXO3a pathway.

[414]

TÍTULO / TITLE: - MAGI2 enhances the sensitivity of BEL-7404 human hepatocellular carcinoma cells to staurosporine-induced apoptosis by increasing PTEN stability.

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

REVISTA / JOURNAL: - Int J Mol Med. 2013 Jun 7. doi: 10.3892/ijmm.2013.1411.

●● Enlace al texto completo (gratis o de pago) [3892/ijmm.2013.1411](#)

AUTORES / AUTHORS: - Li X; Li Z; Li N; Qi J; Fan K; Yin P; Zhao C; Liu Y; Yao W; Cai X; Wang L; Zha X

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, School of Basic Medical Science, Fudan University, Shanghai 200032, P.R. China.

RESUMEN / SUMMARY: - Adaptor proteins are involved in the assembly of various intracellular complexes and the regulation of cellular functions. Membrane-associated guanylate kinase inverted 2 (MAGI2), also known as synaptic scaffolding molecule (S-SCAM), plays a critical role in signal transduction by assembling and anchoring its ligands. However, the role of MAGI2 in mediating apoptosis remains largely unknown. In the present study, BEL-7404 human hepatocellular carcinoma cells were transfected with a plasmid containing myc-MAGI2 or an empty plasmid and cell viability was then determined using the Cell Counting kit-8. Apoptosis was also detected using an Annexin V apoptosis assay. The cells were then treated with various doses of staurosporine (STS) for different periods of time. The overexpression of myc-MAGI2 was found to sensitize the BEL-7404 cells to apoptosis in response to STS in a time- and dose-dependent manner. Our results demonstrated that MAGI2 enhanced STS-induced apoptosis by increasing the protein expression of cytoplasmic phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and decreasing its protein degradation. The apoptotic sensitivity of the cells caused by the overexpression of myc-MAGI2 was reversed by the silencing of PTEN expression by PTEN siRNA, thus revealing a momentous role of PTEN in the enhancement of the sensitivity of cancer cells to STS-induced apoptosis by MAGI2. Finally, we observed that the MAGI-PTEN complex triggered by MAGI2 overexpression reduced the phosphorylation levels of AKT. These results suggest that MAGI2 overexpression enhances the sensitivity of cancer cells harboring ectopic PTEN to STS-induced apoptosis.

[415]

TÍTULO / TITLE: - Bengalin initiates autophagic cell death through ERK-MAPK pathway following suppression of apoptosis in human leukemic U937 cells.

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

REVISTA / JOURNAL: - Life Sci. 2013 Jul 11. pii: S0024-3205(13)00376-7. doi: 10.1016/j.lfs.2013.06.022.

●● Enlace al texto completo (gratis o de pago) [1016/j.lfs.2013.06.022](#)

AUTORES / AUTHORS: - Das Gupta S; Halder B; Gomes A; Gomes A

INSTITUCIÓN / INSTITUTION: - Drug Development/Diagnostics and Biotechnology Division, Council of Scientific and Industrial Research (CSIR)-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata-700032, India.

RESUMEN / SUMMARY: - AIMS: The aim of this study was to assess the autophagy inducing ability of the scorpion venom toxin Bengalin in human leukemic U937 cells. The same toxin was previously shown to induce apoptosis in human leukemic cells. MAIN METHODS: Bengalin was purified from Indian black scorpion (*Heterometrus bengalensis*) venom by ion exchange chromatography and HPLC. In human leukemic U937 cells, Bengalin associated MAPK (mitogen activated protein kinase) pathway was determined by western blotting. Downstream to MAPK, the Bengalin induced apoptosis-

mediator caspase-3 was blocked by chemical inhibitor and reconfirmed by siRNA mediated gene knockdown. Subsequent to caspase-3 blocking, the autophagic response was evaluated by quantification of acidic vesicle organelles formation and modulations of Atg's, Beclin-1, LC3-I and LC3-II expression by western blotting. **KEY FINDINGS:** In U937 cells, Bengalin increased ERK1/2 expression to bring about cell death. However in subsequent caspase-3 blocked conditions, Bengalin downregulated p-Akt, p-mTOR and decreased apoptosis. It had also increased the percentage of acidic vesicle organelles positive cells. Bengalin could induce autophagic response by augmenting Beclin-1, Atg12, Atg7, Atg5 and Atg3 in U937 cells. Moreover a time dependant reciprocal relation was observed between LC3-I and LC3-II expression upon Bengalin treatment. The decrease in LC3-II was inhibited in the presence of lysosomal enzyme blockers thereby suggesting lysosome involvement in the autophagic response. **SIGNIFICANCE:** We have for the first time demonstrated that scorpion venom-component could induce an alternate cell death pathway other than apoptosis in the form of autophagy in human leukemic U937 cells.

[416]

TÍTULO / TITLE: - Dihydrotanshinone induces p53-independent but ROS-dependent apoptosis in colon cancer cells.

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

REVISTA / JOURNAL: - Life Sci. 2013 Jul 19. pii: S0024-3205(13)00394-9. doi: 10.1016/j.lfs.2013.07.007.

●● Enlace al texto completo (gratis o de pago) [1016/j.lfs.2013.07.007](#)

AUTORES / AUTHORS: - Wang L; Yeung JH; Hu T; Lee WY; Lu L; Zhang L; Shen J; Chan RL; Wu WK; Cho CH

INSTITUCIÓN / INSTITUTION: - Faculty of Medicine, School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China.

RESUMEN / SUMMARY: - AIMS: The therapeutic potential of various tanshinones was examined and compared for their anti-cancer activities on colon cancer cells. The role of ROS generation in the pro-apoptotic activity of dihydrotanshinone (DHTS) was further studied. **MAIN METHODS:** Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Apoptosis and poly-ADP-ribose-polymerase (PARP) cleavage were respectively measured by flow cytometer and Western blot. Changes of mitochondrial membrane potential (MMP), mitochondrial ROS (mitoROS) and total ROS were determined by confocal system under an inverted microscope. **KEY FINDINGS:** Among the different tanshinones examined, DHTS produced the most potent anti-cancer effect. DHTS induced a selective cytotoxicity and apoptosis in both HCT116 p53^{-/-} and HCT116 p53^{+/+} colon cancer cells. A time- and concentration-dependent PARP cleavage further confirmed the apoptotic activity. In this regard, it was found DHTS provoked

mitochondrial dysfunction in the early stage by decreasing MMP and mitoROS levels. This was followed by a time-dependent increase in intracellular ROS generation. Pretreatment with N-acetyl-L-cysteine (NAC) or catalase-PEG, the free radical scavengers, reduced apoptotic cell death. From these findings, it seems that leakage of ROS from mitochondria into cytosol by DHTS represents the major contributory factor leading to cell death in colon cancer cells.

SIGNIFICANCE: We report for the first time that DHTS induces apoptosis in colon cancer cells through a p53-independent pathway. Disturbance of ROS generation at the oxidative phosphorylation (OXPHOS) complex in mitochondria followed by the decrease of MMP and increase of intracellular ROS accumulation are suggested to be involved in the pro-apoptotic activity of DHTS.

[417]

TÍTULO / TITLE: - Effect of the pesticide, deltamethrin, on Ca signaling and apoptosis in OC2 human oral cancer cells.

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

REVISTA / JOURNAL: - Drug Chem Toxicol. 2013 Jul 5.

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

[3109/01480545.2013.806528](#)

AUTORES / AUTHORS: - Chi CC; Chou CT; Liang WZ; Jan CR

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - Abstract Deltamethrin is a synthetic pyrethroid insecticide used extensively in pest control. Although deltamethrin has been shown to induce cytosolic free Ca²⁺ concentration ([Ca²⁺]_i) rises and apoptosis in different cancer cells, there is no information concerning the effects of deltamethrin on oral cancer. This study explored the effects of deltamethrin on [Ca²⁺]_i and viability in OC2 human oral cancer cells. Deltamethrin, at concentrations of 5-10 μM, increased [Ca²⁺]_i in a concentration-dependent manner. The Ca²⁺ signal was reduced partly by removing extracellular Ca²⁺. Deltamethrin-induced [Ca²⁺]_i rise was not inhibited by econazole, SK&F96365, phorbol 12-myristate 13 acetate (PMA) or GF109203X, but was inhibited by nifedipine. In Ca²⁺-free medium, 10-μM deltamethrin pretreatment inhibited the [Ca²⁺]_i rise induced by the endoplasmic reticulum Ca²⁺ pump inhibitor, 2,5-di-tert-butylhydroquinone (BHQ). Conversely, pretreatment with BHQ inhibited deltamethrin-induced [Ca²⁺]_i rise. Inhibition of inositol 1,4,5-trisphosphate formation with phospholipase C (PLC) inhibitor U73122 did not suppress deltamethrin-induced Ca²⁺ release. At concentrations between 20 and 100 μM, deltamethrin killed cells in a concentration-dependent manner. The cytotoxic effect of deltamethrin was not reversed by prechelating cytosolic Ca²⁺ with 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid/acetoxymethyl. Deltamethrin-induced cell death was not caused by a preceding [Ca²⁺]_i rise.

Annexin V/propidium iodide staining data suggest that deltamethrin (40-60 μM) induced apoptosis in a concentration-dependent manner. To conclude, in OC2 cells, deltamethrin evoked a $[\text{Ca}^{2+}]_i$ rise by inducing PLC-independent Ca^{2+} release from the endoplasmic reticulum and Ca^{2+} entry by nifedipine-sensitive Ca^{2+} channels. Further, deltamethrin induced Ca^{2+} -independent cell death might involve apoptosis.

[418]

TÍTULO / TITLE: - AdHu5-apoptin induces G2/M arrest and apoptosis in p53-mutated human gastric cancer SGC-7901 cells.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0936-](#)

[3](#)

AUTORES / AUTHORS: - Li Q; Zhang H; Tan C; Peng W; Ren G; Jia B; He Y; Wang P; Zhou X; Xiang T

INSTITUCIÓN / INSTITUTION: - Molecular Oncology and Epigenetics Laboratory, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

RESUMEN / SUMMARY: - The use of anticancer therapeutic agents is limited largely by their severe toxicity to normal tissues. The development of novel agents with tumor-specific cell-killing and effective gene delivery properties is thus very desirable. We used human adenovirus serotype 5 (AdHu5) as a vehicle to deliver the apoptin gene to specifically target gastric cancer in a recombinant gene delivery approach. AdHu5-apoptin is a safe and efficacious agent for the treatment of gastric cancer (GC). Our results show that apoptin protein encoded by the apoptin gene delivered via AdHu5 significantly inhibited the proliferation of SGC-7901 GC cells. Apoptin reduced the clone number by more than 75 % and resulted in cell cycle arrest in the G2/M phase for 48 % of the GC cells. It also induced cleavage of caspase-3, caspase-7, and caspase-9 in the GC cells. Intratumoral and peritumoral in vivo injection of AdHu5-apoptin significantly suppressed tumor growth and induced apoptosis in xenogeneic tumors in mice. The apoptosis induced by AdHu5-apoptin was independent of anti-apoptotic Bcl-2 and Bcl-xL proteins and the p53 pathway. Taken together, our results show that AdHu5-apoptin has great potential as a therapeutic agent for effective treatment of gastric tumors.

[419]

TÍTULO / TITLE: - The value of the pretreatment albumin/globulin ratio in predicting the long-term survival in colorectal cancer.

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

REVISTA / JOURNAL: - Int J Colorectal Dis. 2013 Jul 16.

- Enlace al texto completo (gratis o de pago) [1007/s00384-013-1748-](https://doi.org/10.1007/s00384-013-1748-z)

[Z](#)

AUTORES / AUTHORS: - Azab B; Kedia S; Shah N; Vonfrolio S; Lu W; Naboush A; Mohammed F; Bloom SW

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY, 10305, USA, basemnady2000@yahoo.com.

RESUMEN / SUMMARY: - BACKGROUND: Low serum albumin was found as a predictor of long-term mortality in colorectal cancer (CRC) patients. Our aim was to evaluate the value of the pretreatment albumin/globulin ratio (AGR) to predict the long-term mortality in CRC patients. METHODS: Patients were included if they had comprehensive metabolic panel (CMP) before treatment (surgery or chemotherapy). The albumin/globulin ratio, routinely reported in CMP, is calculated [AGR = Albumin/(Total protein - Albumin)]. Patients were divided into three equal tertiles according to their pretreatment AGR. The primary outcome was cancer-related mortality, which was obtained from our cancer registry database. RESULTS: A total of 534 consecutive CRC patients had pretreatment CMP. The 1st AGR tertile had a significant higher 4-year mortality compared to the second and third AGR tertiles (42 vs. 19 and 7 %, $p < 0.0001$ according to Fisher's exact two-tailed test). In the multivariate model, AGR remained an independent predictor of survival with 75 % decrease in mortality among the highest AGR tertile in comparison to the lowest AGR tertile, $p < 0.0001$. In the subset of 234 patients with normal serum albumin (albumin of >3.5 g/dl), serum AGR continues to be an independent predictor of cancer-related mortality with an adjusted hazard ratio of the third tertile compared to the first tertile equal to 0.05 (95 % confidence interval 0.01-0.33, $p = 0.002$). CONCLUSION: Low AGR was a strong independent predictor of long-term cancer-specific survival among colorectal cancer patients. Additionally, among the patients with normal albumin (>3.5 g/dl), patients with lower globulins but higher albumin and AGR levels had better survival.

[420]

TÍTULO / TITLE: - Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 13. doi: 10.1002/ijc.28387.

- Enlace al texto completo (gratis o de pago) [1002/ijc.28387](https://doi.org/10.1002/ijc.28387)

AUTORES / AUTHORS: - Roepman P; Schlicker A; Tabernero J; Majewski I; Tian S; Moreno V; Snel MH; Chresta CM; Rosenberg R; Nitsche U; Macarulla T; Capella G; Salazar R; Orphanides G; Wessels LF; Bernards R; Simon I

INSTITUCIÓN / INSTITUTION: - Department of Research and Development, Agendia NV, Amsterdam, the Netherlands.

RESUMEN / SUMMARY: - In most colorectal cancer (CRC) patients, outcome cannot be predicted because tumors with similar clinicopathological features can have differences in disease progression and treatment response. Therefore a better understanding of the CRC biology is required to identify those patients who will benefit from chemotherapy and to find a more tailored therapy plan for other patients. Based on unsupervised classification of whole genome data from 188 stage I-IV CRC patients, a molecular classification was developed that consist of at least three major intrinsic subtypes (A-, B-, C-type). The subtypes were validated in 543 stage II-III patients and were associated with prognosis and benefit from chemotherapy. The heterogeneity of the intrinsic subtypes is largely based on 3 biological hallmarks of the tumor: epithelial-to-mesenchymal transition, deficiency in mismatch repair genes that result in high mutation frequency associated with MSI, and cellular proliferation. A-type tumors, observed in 22% of the patients, have the best prognosis, have frequent BRAF mutations and a deficient DNA mismatch repair system. C-type patients (16%) have the worst outcome, a mesenchymal gene expression phenotype, and show no benefit from adjuvant chemotherapy treatment. Both A-type and B-type tumors have a more proliferative and epithelial phenotype and B-types benefit from adjuvant chemotherapy. B-type tumors (62%) show a low overall mutation frequency consistent with the absence of DNA mismatch repair deficiency. Classification based on molecular subtypes made it possible to expand and improve CRC classification beyond standard molecular and immunohistochemical assessment and might help in the future to guide treatment in CRC patients. © 2013 Wiley Periodicals, Inc.

[421]

TÍTULO / TITLE: - In papillary thyroid carcinoma, TIMP-1 expression correlates with BRAF mutation status and together with hypoxia-related proteins predicts aggressive behavior.

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

REVISTA / JOURNAL: - Virchows Arch. 2013 Jul 27.

- Enlace al texto completo (gratis o de pago) [1007/s00428-013-1453-](http://1007/s00428-013-1453-x)

[X](#)

AUTORES / AUTHORS: - Ilie MI; Lassalle S; Long-Mira E; Hofman V; Zangari J; Benaim G; Bozec A; Guevara N; Haudebourg J; Birtwisle-Peyrottes I; Santini J; Brest P; Hofman P

INSTITUCIÓN / INSTITUTION: - Laboratory of Clinical and Experimental Pathology, Louis Pasteur Hospital, 30 Voie Romaine, 06001, Nice Cedex 01, France.

RESUMEN / SUMMARY: - BRAF V600E causes upregulation of tissue inhibitor of metalloproteinase-1 (TIMP-1), which promotes cell invasion in papillary thyroid carcinoma (PTC). Hypoxia-inducible factor-1alpha (HIF-1alpha) is regulated by hypoxia and also by the BRAF-mediated signaling pathway in PTC. We assessed the association of expression of TIMP-1, HIF-1alpha, and hypoxia-

inducible carbonic anhydrase IX (CAIX) and XII (CAXII) with clinical parameters in PTC. TPC-1/BRAF WT wild-type and BcPAP/BRAF V600E -mutated PTC cell lines were selected to study the effects of the BRAF V600E mutation and hypoxia on expression in vitro of TIMP-1, CAIX, and CAXII proteins by immunoblotting. Higher expression of all proteins was detected in BcPAP cells exposed to hypoxia. Tissue microarray immunohistochemistry analysis was performed to study protein expression in 114 BRAF-genotyped PTC samples. Expression data on tumor tissue were compared with clinicopathological variables. TIMP-1 expression had a sensitivity of 87 % and a specificity of 83 % in identifying a BRAF mutation ($P < 0.001$) and was associated with pT stage ($P = 0.001$), pN stage ($P = 0.02$), and multifocality ($P = 0.03$). HIF-1alpha expression correlated with pT stage ($P = 0.05$). CAIX expression was associated with pN stage ($P = 0.02$), and both CAIX ($P = 0.004$) and CAXII ($P = 0.05$) were strongly associated with vascular invasion. We conclude that TIMP-1 protein expression is a reliable surrogate marker for BRAF-mutated status in PTC. TIMP-1 and hypoxia-regulated proteins are promising as predictors of aggressiveness in PTC and warrant further investigation as new therapeutic targets for the treatment of highly aggressive forms of PTC.

[422]

TÍTULO / TITLE: - Tissue transglutaminase mediates the pro-malignant effects of oncostatin M receptor over-expression in cervical squamous cell carcinoma.

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

REVISTA / JOURNAL: - J Pathol. 2013 Jun 13. doi: 10.1002/path.4222.

●● Enlace al texto completo (gratis o de pago) [1002/path.4222](#)

AUTORES / AUTHORS: - Caffarel MM; Chattopadhyay A; Araujo AM; Bauer J; Scarpini CG; Coleman N

INSTITUCIÓN / INSTITUTION: - Department of Pathology, University of Cambridge, UK.

RESUMEN / SUMMARY: - Oncostatin M receptor (OSMR) is commonly over-expressed in advanced cervical squamous cell carcinoma (SCC), producing a significantly worse clinical outcome. Cervical SCC cells that over-express OSMR show enhanced responsiveness to the major ligand OSM, which induces multiple pro-malignant effects, including increased cell migration and invasiveness. Here, we show that tissue transglutaminase (TGM2) is an important mediator of the ligand-dependent phenotypic effects of OSMR over-expression in SCC cells. TGM2 expression correlated with disease progression and with OSMR levels in clinical samples of cervical and oral SCC. TGM2 depletion in cervical SCC cells abrogated OSM-induced migration on fibronectin-coated surfaces and invasiveness through extracellular matrix, while ectopic expression of TGM2 increased cell motility and invasiveness. Confocal microscopy and co-immunoprecipitation assays showed that TGM2 interacted with integrin- $\alpha 5\beta 1$ in the presence of fibronectin in cervical SCC cells,

with OSM treatment strengthening the interaction. Importantly, integrin- $\alpha 5\beta 1$ and fibronectin were also over-expressed in cervical and oral SCC, where levels correlated with those of OSMR and TGM2. This combined tissue and in vitro study demonstrates for the first time that stimulation of over-expressed OSMR in cervical SCC cells activates TGM2:integrin- $\alpha 5\beta 1$ interactions and induces pro-malignant changes. We conclude that an OSMR/TGM2/integrin- $\alpha 5\beta 1$ /fibronectin pathway is of biological significance in cervical SCC and a candidate for therapeutic targeting.

[423]

TÍTULO / TITLE: - Interleukin-22 Is Frequently Expressed in Small- and Large-Cell Lung Cancer and Promotes Growth in Chemotherapy-Resistant Cancer Cells.

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

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug;8(8):1032-1042.

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

[1097/JTO.0b013e31829923c8](#)

AUTORES / AUTHORS: - Kobold S; Volk S; Clauditz T; Kupper NJ; Minner S; Tufman A; Duwell P; Lindner M; Koch I; Heidegger S; Rothenfuer S; Schnurr M; Huber RM; Wilczak W; Endres S

INSTITUCIÓN / INSTITUTION: - *Department of Internal Medicine IV, Division of Clinical Pharmacology and Center of Integrated Protein Science, Ludwig-Maximilians Universität München, Member of the German Center for Lung Research, Munich, Germany; daggerInstitute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Departments of double daggerInternal Medicine V, Thoracic Oncology Center, section signInternal Medicine IV, Munich, Ludwig-Maximilians Universität München, Munich, Germany, Member of the German Center for Lung Research; and ||Center for Thoracic Surgery, Asklepios Biobank for Lung Diseases, Asklepios Clinic München-Gauting, Comprehensive Pneumology Center Munich, München-Gauting, Germany, Member of the German Center for Lung Research.

RESUMEN / SUMMARY: - INTRODUCTION:: In lung cancer, interleukin-22 (IL-22) expression within primary tissue has been demonstrated, but the frequency and the functional consequence of IL-22 signaling have not been addressed. This study aims at analyzing the cellular effects of IL-22 on lung carcinoma cell lines and the prognostic impact of IL-22 tissue expression in lung cancer patients. METHODS:: Biological effects of IL-22 signaling were investigated in seven lung cancer cell lines by Western blot, flow cytometry, real-time polymerase chain reaction, and proliferation assays. Tumor tissue specimens of two cohorts with a total of 2300 lung cancer patients were tested for IL-22 expression by immunohistochemistry. IL-22 serum concentrations were analyzed in 103 additional patients by enzyme-linked immunosorbent assay. RESULTS:: We found the IL-22 receptor 1 (IL-22-R1) to be expressed in six of seven lung

cancer cell lines. However IL-22 signaling was functional in only four cell lines, where IL-22 induced signal transducer activator of transcription 3 phosphorylation and increased cell proliferation. Furthermore, IL-22 induced the expression of antiapoptotic B-cell lymphoma 2, but did not rescue tumor cells from carboplatin-induced apoptosis. Cisplatin-resistant cell lines showed a significant up-regulation of IL-22-R1 along with a stronger proliferative response to IL-22 stimulation. IL-22 was preferentially expressed in small- and large-cell lung carcinoma (58% and 46% of cases, respectively). However, no correlation between IL-22 expression by immunohistochemistry and prognosis was observed. CONCLUSION:: IL-22 is frequently expressed in lung cancer tissue. Enhanced IL-22-R1 expression and signaling in chemotherapy-refractory cell lines are indicative of a protumorigenic function of IL-22 and may contribute to a more aggressive phenotype.

[424]

TÍTULO / TITLE: - Evodiamine, a plant alkaloid, induces calcium/JNK-mediated autophagy and calcium/mitochondria-mediated apoptosis in human glioblastoma cells.

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

REVISTA / JOURNAL: - Chem Biol Interact. 2013 Jun 15;205(1):20-28. doi: 10.1016/j.cbi.2013.06.004.

●● Enlace al texto completo (gratis o de pago) [1016/j.cbi.2013.06.004](#)

AUTORES / AUTHORS: - Liu AJ; Wang SH; Chen KC; Kuei HP; Shih YL; Hou SY; Chiu WT; Hsiao SH; Shih CM

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; Department of Neurosurgery, Taipei City Hospital Ren-Ai Branch, Taipei, Taiwan, ROC.

RESUMEN / SUMMARY: - Glioblastomas, the most common primary gliomas, are characterized by increased invasion and difficult therapy. Major clinical medicines for treating gliomas merely extend the survival time for a number of months. Therefore, development of new agents against gliomas is important. Autophagy, a process for degrading damaged organelles and proteins, is an adaptive response to environmental stress. However, the role of autophagy in glioblastoma development still needs to be further investigated. Evodiamine, a major alkaloid isolated from *Evodia rutaecarpa* Benth, has various pharmacological activities, such as inhibiting tumor growth and metastatic properties. However, the effects of evodiamine on glioblastomas and their detailed molecular mechanisms and autophagy formation are not well understood. In this study, we observed that evodiamine induced dose- and time-dependent apoptosis in glioma cells. Blockade of calcium channels in endoplasmic reticulum (ER) significantly reduced evodiamine-induced cytosolic calcium elevation, apoptosis, and mitochondrial depolarization, which suggests that evodiamine induces a calcium-mediated intrinsic apoptosis pathway.

Interestingly, autophagy was also enhanced by evodiamine, and had reached a plateau by 24h. Pharmacological inhibition of autophagy resulted in increased apoptosis and reduced cell viability. Inhibition of ER calcium channel activation also significantly reduced evodiamine-induced autophagy. Inactivation of c-Jun N-terminal kinases (JNK) suppressed evodiamine-mediated autophagy accompanied by increased apoptosis. Furthermore, evodiamine-mediated JNK activation was abolished by BAPTA-AM, an intracellular calcium scavenger, suggesting that evodiamine mediates autophagy via a calcium-JNK signaling pathway. Collectively, these results suggest that evodiamine induces intracellular calcium/JNK signaling-mediated autophagy and calcium/mitochondria-mediated apoptosis in glioma cells.

[425]

TÍTULO / TITLE: - INTERLEUKIN-2 AND LANREOTIDE IN THE TREATMENT OF MEDULLARY THYROID CANCER: IN VITRO AND IN VIVO STUDIES.

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

REVISTA / JOURNAL: - J Clin Endocrinol Metab. 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [1210/jc.2013-1443](#)

AUTORES / AUTHORS: - Vitale G; Lupoli G; Guarrasi R; Colao A; Dicitore A; Gaudenzi G; Misso G; Castellano M; Addeo R; Facchini G; Del Prete S; Caraglia M

INSTITUCIÓN / INSTITUTION: - 1Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

RESUMEN / SUMMARY: - Context:No efficacious treatments are to date available for advanced medullary thyroid carcinoma (MTC).Objective:We investigated in vitro and in vivo a new strategy for the therapy of MTC, combining human recombinant interleukin 2 (IL-2) with lanreotide (LAN), a somatostatin analog.Methods:The in vitro effects of LAN on the sensitivity of TT cells, a MTC cell line, to IL-2-stimulated human peripheral blood mononuclear cells (PBMC) have been determined by lactate-dehydrogenase (LDH)-release assay. In addition, we evaluated the toxicity, the effects on quality of life (QoL) and the antitumor activity of subcutaneous low dose IL-2 in combination with LAN (90 mg every 28 days) in a series of six patients with symptomatic and advanced MTC.Results:The cytotoxicity of IL-2-activated PBMC was significantly increased in TT cells treated with LAN or LAN plus IL-2, compared to TT cells without treatment. The therapy was well tolerated and a statistically significant improvement of the QoL was observed in patients treated with the combination of LAN and IL-2. After 6 months of therapy, partial response and stable disease have been recorded in two and three patients, respectively, with a significant decrease in calcitonin levels in three cases.Conclusions:Several in vitro and in vivo evidences suggest that the combination of LAN and IL-2 may have a role in the management of advanced and symptomatic MTC. However, these preliminary data require further validation in larger randomized trials.

[426]

TÍTULO / TITLE: - Genetic Polymorphisms Predicting Methotrexate Blood Levels and Toxicity in Adult Non-Hodgkin's Lymphoma.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 5.

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

[3109/10428194.2013.789506](#)

AUTORES / AUTHORS: - Avivi I; Zuckerman T; Krivoy N; Efrati E

RESUMEN / SUMMARY: - Abstract Methotrexate (MTX), a folate antagonist employed for treating a wide range of malignancies, has an extensive inter-patient variability, resulting in unpredictable toxicity. The current study evaluated the impact of single gene polymorphisms (SNPs: rs1801133 and rs1801131 in the MTHFR gene; rs4149056 and rs11045879 in the SLC01B1 gene; and rs2032582 and rs1045642 in the ABCB1 transporter gene) on MTX blood levels and toxicity in samples from 69 diffuse large-cell lymphoma (DLBCL) patients treated with high dose intravenous (HD IV) MTX, > 2 gr/m². None of the studied genotypes were found to be associated with a statistically significant risk for elevated MTX levels at 24-48 hours after completing therapy with MTX. Ancestral alleles (T) for SLC01B1 rs4149056 (T521C) and SLC01B1 rs11045879 (intron C21273886T) were found to be associated with an increased risk for MTX-related toxicity (p<0.05 and p=0.07, respectively), emphasizing the potential importance of employing pharmacogenetic assessment for personalized medicine.

[427]

TÍTULO / TITLE: - Calyxin Y induces hydrogen peroxide-dependent autophagy and apoptosis via JNK activation in human non-small cell lung cancer NCI-H460 cells.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jun 27. pii: S0304-3835(13)00471-0. doi: 10.1016/j.canlet.2013.06.021.

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

[1016/j.canlet.2013.06.021](#)

AUTORES / AUTHORS: - Zhang C; Yang L; Wang XB; Wang JS; Geng YD; Yang CS; Kong LY

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural Medicines, Department of Natural Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China.

RESUMEN / SUMMARY: - Calyxin Y has been recently isolated from *Alpinia katsumadai* which has a folk use as an anti-tumor medicine. Calyxin Y induced caspase-dependent cell death in NCI-H460 cells, and concomitantly, provoked

cytoprotective autophagy with the upregulation of critical Atg proteins. The cleavage of Atg proteins by caspases acted as a switch between autophagy and apoptosis induced by calyxin Y. Intracellular hydrogen peroxide (H₂O₂) production was triggered upon exposure to calyxin Y via the induction of autophagy and apoptosis. We provided evidence that activated JNK was upstream effectors controlling both autophagy and apoptosis in response to elevated H₂O₂. Therefore, our findings demonstrate that calyxin Y serves multiple roles as a promising chemotherapeutic agent that induces H₂O₂-dependent autophagy and apoptosis via JNK activation.

[428]

TÍTULO / TITLE: - Neferine isolated from *Nelumbo nucifera* enhances anti-cancer activities in Hep3B cells: Molecular mechanisms of cell cycle arrest, ER stress induced apoptosis and anti-angiogenic response.

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

REVISTA / JOURNAL: - *Phytomedicine*. 2013 Aug 15;20(11):1013-22. doi: 10.1016/j.phymed.2013.03.024. Epub 2013 Jun 6.

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

[1016/j.phymed.2013.03.024](#)

AUTORES / AUTHORS: - Yoon JS; Kim HM; Yadunandam AK; Kim NH; Jung HA; Choi JS; Kim CY; Kim GD

INSTITUCIÓN / INSTITUTION: - Department of Microbiology, College of Natural Sciences, Pukyong National University, Namgu, Busan 608-737, Republic of Korea.

RESUMEN / SUMMARY: - Hepatocellular carcinoma (HCC) is one of the most aggressive malignant diseases and is highly resistant to conventional chemotherapy. Neferine, a major bisbenzylisoquinoline alkaloid derived from the embryos of *Nelumbo nucifera*, has been reported a few physiological activities. However, the mechanisms of anticancer effects are not well understood and its detailed activities on Hep3B cells have not been determined. Our results suggest that neferine exhibited cytotoxicity against HCC Hep3B cells, but not against HCC Sk-Hep1 and THLE-3, a normal human liver cell line. In addition, consistent with the induction of G1/S phase cell population in flow cytometry, downregulation of c-Myc, cyclin D1, D3, CDK4, E2F-1, as well as dephosphorylation of cdc2 by western blot analysis, as evidenced by the appearance of cell cycle arrest, were observed in Hep3B cells treated with neferine. Our results demonstrated neferine induced ER stress and apoptosis, acting through multiple signaling cascades by the activation of Bim, Bid, Bax, Bak, Puma, caspases-3, -6, -7, -8 and PARP, and the protein expression levels of Bip, calnexin, PDI, calpain-2 and caspase-12 were also upregulated dramatically by neferine treatment. Overexpression of GFP-LC3B by neferine resulted in a diffuse cytosolic GFP fluorescence and the strong fluorescent spots, representing autophagosomes. The significant reduction of the migration

in Hep3B cells and the capillary tube-like formation of HUVECs by neferine were also determined. These observations reveal that the therapeutic potential of neferine in treating HCC Hep3B cells, containing copies of hepatitis B virus (HBV) genomes.

[429]

TÍTULO / TITLE: - Predicting Efficacy of Cancer Cell Killing under Hypoxic Conditions with Single Cell DNA Damage Assay.

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

REVISTA / JOURNAL: - Anal Chem. 2013 Jul 16;85(14):6953-7. doi: 10.1021/ac401543t. Epub 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1021/ac401543t](#)

AUTORES / AUTHORS: - Qiao Y; Ma L

INSTITUCIÓN / INSTITUTION: - NanoScience Technology Center, University of Central Florida, Florida.

RESUMEN / SUMMARY: - The activity of anticancer drugs determined under normal conditions cannot accurately reflect true drug efficacy in a patient, as a tumor is often under low oxygen (hypoxia) conditions. In addition, patient responses to the same therapy can be drastically different due to tumor heterogeneity. This paper describes the use of single cell halo assay for detection and quantification of DNA damage induced by anticancer drugs or radiation under hypoxic conditions. By combining classical halo assay and state-of-the-art microfabrication techniques, this single cell approach allows drug and radiation responses of cancer cells to be determined without population interference. The results from single cell assay indicate a diminished level of DNA damage at hypoxic conditions compared with those at normal conditions at the same drug concentrations or radiation dose, suggesting in vitro preclinical studies of drug and radiation activity can be performed under conditions that mimic physiological conditions of tumors and without population interference.

[430]

TÍTULO / TITLE: - Rational Combination of a MEK Inhibitor, Selumetinib, and the Wnt/Calcium Pathway Modulator, Cyclosporin A, in Preclinical Models of Colorectal Cancer.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4149-62. doi: 10.1158/1078-0432.CCR-12-3140. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3140](#)

AUTORES / AUTHORS: - Spreafico A; Tentler JJ; Pitts TM; Tan AC; Gregory MA; Arcaroli JJ; Klauk PJ; McManus MC; Hansen RJ; Kim J; Micel LN; Selby HM;

Newton TP; McPhillips KL; Gustafson DL; Degregori JV; Messersmith WA; Winn RA; Eckhardt SG

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Division of Medical Oncology, Department of Molecular Biology, Department of Pathology, Pulmonary and Critical Care, University of Colorado; Division of Pediatric Hematology/Oncology, Children's Hospital Colorado, Anschutz Medical Campus, Aurora; and Department of Clinical Sciences, Colorado State University, Fort Collins, Colorado.

RESUMEN / SUMMARY: - **PURPOSE:** The mitogen-activated protein kinase (MAPK) pathway is a crucial regulator of cell proliferation, survival, and resistance to apoptosis. MEK inhibitors are being explored as a treatment option for patients with KRAS-mutant colorectal cancer who are not candidates for EGFR-directed therapies. Initial clinical results of MEK inhibitors have yielded limited single-agent activity in colorectal cancer, indicating that rational combination strategies are needed. **EXPERIMENTAL DESIGN:** In this study, we conducted unbiased gene set enrichment analysis and synthetic lethality screens with selumetinib, which identified the noncanonical Wnt/Ca⁺⁺ signaling pathway as a potential mediator of resistance to the MEK1/2 inhibitor selumetinib. To test this, we used shRNA constructs against relevant WNT receptors and ligands resulting in increased responsiveness to selumetinib in colorectal cancer cell lines. Further, we evaluated the rational combination of selumetinib and WNT pathway modulators and showed synergistic antiproliferative effects in in vitro and in vivo models of colorectal cancer. **RESULTS:** Importantly, this combination not only showed tumor growth inhibition but also tumor regression in the more clinically relevant patient-derived tumor explant (PDTX) models of colorectal cancer. In mechanistic studies, we observed a trend toward increased markers of apoptosis in response to the combination of MEK and WntCa(++) inhibitors, which may explain the observed synergistic antitumor effects. **CONCLUSIONS:** These results strengthen the hypothesis that targeting both the MEK and Wnt pathways may be a clinically effective rational combination strategy for patients with metastatic colorectal cancer. Clin Cancer Res; 19(15); 4149-62. ©2013 AACR.

[431]

TÍTULO / TITLE: - SB365, Pulsatilla saponin D suppresses proliferation and induces apoptosis of pancreatic cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Aug;30(2):801-8. doi: 10.3892/or.2013.2517. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2517](#)

AUTORES / AUTHORS: - Son MK; Jung KH; Lee HS; Lee H; Kim SJ; Yan HH; Ryu YL; Hong SS

INSTITUCIÓN / INSTITUTION: - Department of Drug Development, College of Medicine, Inha University, Sinheungdong, Jung-gu, Incheon 400-712, Republic of Korea.

RESUMEN / SUMMARY: - Pulsatilla koreana has been used as a traditional medicine for the treatment of various diseases. The purpose of this study was to determine whether SB365, Pulsatilla saponin D isolated from the root of Pulsatilla koreana inhibits the progression of pancreatic cancer. We found that SB365 strongly suppressed the growth and proliferation of 5 human pancreatic cancer cell lines (MIAPaCa-2, BXPC-3, PANC-1, AsPC-1 and HPAC). The apoptotic effect of SB365 was demonstrated by increased levels of cleaved caspase-3 and decreased Bcl-2 expression via mitochondrial membrane potential, as well as elevated numbers of terminal deoxynucleotidyl-transferase-mediated dUTP nick end labeling (TUNEL)-positive apoptotic cells. SB365 was also found to exert an anti-angiogenic effect by decreasing the expression of HIF-1alpha and VEGF, major factors of angiogenesis, which was confirmed by the suppression of tumor sphere formation of pancreatic cancer cells. An in vivo mouse xenograft study showed that SB365 significantly inhibited tumor growth through the induction of apoptosis and inhibition of angiogenesis with strong anticancer activity. Therefore, SB365 is a good candidate as a natural product for use in the treatment of pancreatic cancer.

[432]

TÍTULO / TITLE: - Sick cell trait is not associated with endemic burkitt lymphoma: An ethnicity and malaria endemicity matched case-control study suggests factors controlling EBV may serve as a predictive biomarker for this pediatric cancer.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 5. doi: 10.1002/ijc.28378.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28378](#)

AUTORES / AUTHORS: - Mulama DH; Bailey JA; Foley J; Chelimo K; Ouma C; Jura WG; Otieno J; Vulule J; Moormann AM

INSTITUCIÓN / INSTITUTION: - Center for Global Health Research, Kenyan Medical Research Institute, Kisumu, Kenya; Department of Biomedical Sciences and Technology, Maseno University, Maseno, Kenya.

RESUMEN / SUMMARY: - Endemic Burkitt lymphoma (eBL) is associated with Epstein-Barr Virus (EBV) and Plasmodium falciparum co-infections. Malaria appears to dysregulate immunity that would otherwise control EBV thereby contributing to eBL etiology. Juxtaposed to human genetic variants associated with protection from malaria, it has been hypothesized that such variants could decrease eBL susceptibility, historically referred to as 'the protective hypothesis'. Past studies attempting to link sickle cell trait (HbAS), which is known to be protective against malaria, with protection from eBL were contradictory and underpowered. Therefore, using a case-control study design

we examined HbAS frequency in 306 Kenyan children diagnosed with eBL compared to 537 geographically-defined and ethnically-matched controls. We found 23.8% HbAS for eBL patients which was not significantly different compared to 27.0% HbAS for controls (OR = 0.85 [95% CI, 0.61-1.17]; p-value = 0.33). Even though cellular EBV titers, indicative of the number of latently infected B cells, were significantly higher (p-value < 0.0003) in children residing in malaria holoendemic compared to hypoendemic areas, levels were not associated with HbAS genotype. Combined, this suggests that while HbAS protects against severe malaria and hyper-parasitemia, it is not associated with viral control or eBL protection. However, based on receiver operating characteristic (ROC) curves factors that enable the establishment of EBV persistence, in contrast to those involved in EBV lytic reactivation, may have utility as an eBL precursor biomarker. This has implications for future human genetic association studies to consider variants influencing control over EBV in addition to malaria as risk factors for eBL. © 2013 Wiley Periodicals, Inc.

[433]

TÍTULO / TITLE: - Interleukin-6 and JAK2/STAT3 signaling mediate the reversion of dexamethasone resistance after dexamethasone withdrawal in 7TD1 multiple myeloma cells.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Jul 18. pii: S0145-2126(13)00226-9. doi: 10.1016/j.leukres.2013.06.026.

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

[1016/j.leukres.2013.06.026](#)

AUTORES / AUTHORS: - Liu T; Fei Z; Gangavarapu KJ; Agbenowu S; Bhushan A; Lai JC; Daniels CK; Cao S

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Division of Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA.

RESUMEN / SUMMARY: - We previously reported the establishment and characteristics of a DXM-resistant cell line (7TD1-DXM) generated from the IL6-dependent mouse B cell hybridoma, 7TD1 cell line. After withdrawing DXM from 7TD1-DXM cells over 90 days, DXM significantly inhibited the cell growth and induced apoptosis in the cells (7TD1-WD) compared with 7TD1-DXM cells. Additionally, IL-6 reversed while IL-6 antibody and AG490 enhanced the effects of growth inhibition and apoptosis induced by DXM in 7TD1-WD cells. Our study demonstrates that 7TD1-DXM cells become resensitized to DXM after DXM withdrawal, and IL-6 and JAK2/STAT3 pathways may regulate the phenomenon.

[434]

TÍTULO / TITLE: - T-cell apoptosis induced by intratumoral activated hepatic stellate cells is associated with lung metastasis in hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 27. doi: 10.3892/or.2013.2571.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2571](#)

AUTORES / AUTHORS: - Xia YH; Wang ZM; Chen RX; Ye SL; Sun RX; Xue Q; Huang Y

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Hefei Second People's Hospital, Anhui Medical University, Hefei 230011, P.R. China.

RESUMEN / SUMMARY: - Profound T cell inhibitory activity of hepatic stellate cells (HSCs) in vitro has recently been described in hepatocellular carcinoma (HCC). In the present study, we investigated the immune inhibitory activity of HSCs in vivo in an orthotopic rat HCC model with lung metastasis. Rats (n=24) were randomly sacrificed on days 7, 14, 21 and 28 (n=4 each). Lung tissues were stained with hematoxylin and eosin. Liver sections were stained for immunofluorescence analysis. T-cell apoptosis was detected using double staining for terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL). Staining revealed marked and continuous accumulation of alpha-smooth muscle actin with tumor progression after orthotopic tumor implantation in rat liver. T lymphocyte numbers gradually increased following tumor progression, and subset analysis revealed an increase in the distribution of liver CD8+ and CD4+ T cells. Double staining for CD3 and TUNEL demonstrated T-cell apoptosis. Apoptotic T cells were more frequent in the HCC livers compared to the normal livers, and were spatially associated with intratumoral activated HSCs (tHSCs), suggesting a direct interaction. T-cell apoptosis was more frequently induced in the co-cultures of activated splenic T cells(aT)/tHSCs compared to aT/quiescent (q) HSCs or qT/tHSCs. tHSCs were positively correlated with T-cell apoptosis, and the percentage of T-cells undergoing apoptosis was positively correlated with the number of lung metastasis nodules. T-cell apoptosis may be promoted via an interaction with tHSCs, suggesting that tHSCs regulate T cells and contribute to lung metastasis in HCC.

[435]

TÍTULO / TITLE: - Selective induction of apoptosis in various cancer cells irrespective of drug sensitivity through a copper chelate, copper N-(2 hydroxy acetophenone) glycinate: crucial involvement of glutathione.

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

REVISTA / JOURNAL: - Biometals. 2013 Jun;26(3):517-34. doi: 10.1007/s10534-013-9637-z. Epub 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1007/s10534-013-9637-](#)

[z](#)

AUTORES / AUTHORS: - Chatterjee S; Chakraborty P; Banerjee K; Sinha A; Adhikary A; Das T; Choudhuri SK

INSTITUCIÓN / INSTITUTION: - Department of In Vitro Carcinogenesis and Cellular Chemotherapy, Chittaranjan National Cancer Institute, S.P. Mukherjee Road, Kolkata 700026, India.

RESUMEN / SUMMARY: - Drug induced toxicity and drug resistance are the major impediments to successful application of cancer chemotherapy. Therefore, selective targeting of the key biochemical events of the malignant cells may have a great therapeutic potential in specifically kill the cancer cells. We have evaluated in vitro the cytotoxic efficacy of a previously reported copper complex viz. copper N-(2-hydroxy acetophenone) glycinate (CuNG) on different drug sensitive and resistant cancer cell lines by MTT, annexin V positivity and caspase 3 activation assays. We have also investigated the underlying signalling events in CuNG mediated apoptosis of cancer cells by Western blotting technique. We have found that CuNG preferentially induces apoptosis to malignant cells irrespective of drug sensitivity and spares the normal cells. Our studies disclose that CuNG causes cellular redox imbalance in cancer cells through depletion of intracellular GSH level. CuNG mediated depletion of intracellular GSH level induces mitochondrial superoxide generation, which detaches cyto C from mitochondrial membrane through lipid peroxidation. The detached cyto C then release into the extra mitochondrial milieu in Bax mediated pathway where CuNG facilitates the binding of Bax through dissociation of hexokinase II from mitochondrial membrane. The present study opens the possibility of developing effective chemotherapeutic drugs by synthesizing numerous chemical compounds capable of targeting cellular redox environment and thus specifically kills cancer cells of broad spectrum.

[436]

TÍTULO / TITLE: - Interaction between docetaxel resistance and castration resistance in prostate cancer: Implications of Twist1, YB-1, and androgen receptor.

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

REVISTA / JOURNAL: - Prostate. 2013 Sep;73(12):1336-44. doi: 10.1002/pros.22681. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22681](#)

AUTORES / AUTHORS: - Shiota M; Kashiwagi E; Yokomizo A; Takeuchi A; Dejima T; Song Y; Tatsugami K; Inokuchi J; Uchiumi T; Naito S

INSTITUCIÓN / INSTITUTION: - Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Taxanes, including docetaxel, are currently the only cytotoxic chemotherapeutic agents proven to confer survival benefit in patients with castration-resistant prostate cancer (CRPC). However, the merits of taxanes remain modest, and efforts are needed to improve their

therapeutic efficacy. **METHODS:** We evaluated the sensitivity of prostate cancer cells to various agents using cytotoxicity assays. Gene and protein expression levels were evaluated by quantitative real-time polymerase chain reaction and Western blotting analysis, respectively. **RESULTS:** Hydrogen peroxide-resistant and castration-resistant cells that overexpressed Twist1 and Y-box binding protein-1 (YB-1) were cross-resistant to cytotoxic agents, including docetaxel. Twist1 regulated YB-1 expression in prostate cancer cells, supported by the induction of Twist1 and YB-1 by transforming-growth factor-beta, which is critical for taxane resistance. Twist1 and/or YB-1 were activated in docetaxel-resistant prostate cancer cells, and YB-1 was activated by docetaxel treatment. Conversely, Twist1 and YB-1 knockdown sensitized prostate cancer cells to cytotoxic agents, including docetaxel. In addition, androgen receptor (AR) knockdown increased cellular sensitivity to docetaxel, though AR expression in docetaxel-resistant LNCaP cells was paradoxically lower than in parental cells. Intriguingly, androgen deprivation treatment was more effective in docetaxel-resistant LNCaP cells compared with parental cells. **CONCLUSIONS:** Twist1/YB-1 and AR signaling promote docetaxel resistance in CRPC cells. However, docetaxel-resistant cells were collaterally sensitive to androgen deprivation because of down-regulation of AR expression, suggesting that the therapeutic effect of initial taxane treatment in hormone-naive prostate cancer may be superior to that of salvage taxane treatment in CRPC. Prostate 73: 1336-1344, 2013. © 2013 Wiley Periodicals, Inc.

[437]

TÍTULO / TITLE: - Isoliquiritigenin induces growth inhibition and apoptosis through downregulating arachidonic acid metabolic network and the deactivation of PI3K/Akt in human breast cancer.

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

REVISTA / JOURNAL: - Toxicol Appl Pharmacol. 2013 Jun 5. pii: S0041-008X(13)00261-5. doi: 10.1016/j.taap.2013.05.031.

●● Enlace al texto completo (gratis o de pago) [1016/j.taap.2013.05.031](#)

AUTORES / AUTHORS: - Li Y; Zhao H; Wang Y; Zheng H; Yu W; Chai H; Zhang J; Falck JR; Guo AM; Yue J; Peng R; Yang J

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, School of Medicine, Wuhan University, Wuhan 430071, China.

RESUMEN / SUMMARY: - Arachidonic acid (AA)-derived eicosanoids and its downstream pathways have been demonstrated to play crucial roles in growth control of breast cancer. Here, we demonstrate that isoliquiritigenin, a flavonoid phytoestrogen from licorice, induces growth inhibition and apoptosis through downregulating multiple key enzymes in AA metabolic network and the deactivation of PI3K/Akt in human breast cancer. Isoliquiritigenin diminished cell viability, 5-bromo-2'-deoxyuridine (BrdU) incorporation, and clonogenic ability in both MCF-7 and MDA-MB-231 cells, and induced apoptosis as

evidenced by an analysis of cytoplasmic histone-associated DNA fragmentation, flow cytometry and hoechst staining. Furthermore, isoliquiritigenin inhibited mRNA expression of multiple forms of AA-metabolizing enzymes, including phospholipase A2 (PLA2), cyclooxygenases (COX)-2 and cytochrome P450 (CYP) 4^a, and decreased secretion of their products, including prostaglandin E2 (PGE2) and 20-hydroxyeicosatetraenoic acid (20-HETE), without affecting COX-1, 5-lipoxygenase (5-LOX), 5-lipoxygenase activating protein (FLAP), and leukotriene B4 (LTB4). In addition, it downregulated the levels of phospho-PI3K, phospho-PDK (Ser241), phospho-Akt (Thr308), phospho-Bad (Ser136), and Bcl-xL expression, thereby activating caspase cascades and eventually cleaving poly(ADP-ribose) polymerase (PARP). Conversely, the addition of exogenous eicosanoids, including PGE2, LTB4 and a 20-HETE analog (WIT003), and caspase inhibitors, or overexpression of constitutively active Akt reversed isoliquiritigenin-induced apoptosis. Notably, isoliquiritigenin induced growth inhibition and apoptosis of MDA-MB-231 human breast cancer xenografts in nude mice, together with decreased intratumoral levels of eicosanoids and phospho-Akt (Thr308). Collectively, these data suggest that isoliquiritigenin induces growth inhibition and apoptosis through downregulating AA metabolic network and the deactivation of PI3K/Akt in human breast cancer.

[438]

TÍTULO / TITLE: - Ammonium chloride enhances cisplatin cytotoxicity through DNA double-strand breaks in human cervical cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 20. doi: 10.3892/or.2013.2554.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2554](#)

AUTORES / AUTHORS: - Xu Y; Wang N; Ding Y; Wang C; Yu Y; Liu S; Wang X; Li Z

INSTITUCIÓN / INSTITUTION: - Medical Research Laboratory, Jilin Medical College, Jilin 132013, P.R. China.

RESUMEN / SUMMARY: - Cisplatin (cis-diamminedichloroplatinum II, CDDP) acts as a therapeutic agent by initiating cellular apoptosis. However, side-effects and drug resistance limit the clinical use of cisplatin. Numerous studies have focused on the drug-target interactions, cellular pharmacology and pharmacokinetics of cisplatin. Newly developed treatment strategies are needed in order to be used in combination with cisplatin, with the aim to minimize toxicity and to circumvent cisplatin resistance. Ammonium chloride (NH₄Cl) is widely used in various areas, but its use as a combination agent with cisplatin for the treatment of cancer cells has not been previously reported. In the present study, we showed that NH₄Cl could be potentially used as an effective agent in cisplatin combination treatment of HeLa human cervical cancer (HCC) cells. Cisplatin was found to inhibit cell growth, as well as to induce cell

apoptosis and DNA double-strand breaks. In addition, treatment with NH₄Cl increased the rate of cell apoptosis and the activation of caspase-3. Particularly, we found that NH₄Cl treatment increased cisplatin-induced phosphorylation of H2AX. In conclusion, our data indicate that NH₄Cl enhances cisplatin cytotoxicity through increased DNA damage in HeLa HCC cells.

[439]

TÍTULO / TITLE: - Assessment of health-related quality of life predicts the outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C.

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

REVISTA / JOURNAL: - J Gastroenterol Hepatol. 2013 Jul 22. doi: 10.1111/jgh.12337.

●● Enlace al texto completo (gratis o de pago) 1111/jgh.12337

AUTORES / AUTHORS: - Matsushita H; Ikeda F; Iwasaki Y; Seki H; Nanba S; Takeuchi Y; Moritou Y; Yasunaka T; Onishi H; Miyake Y; Takaki A; Nouse K; Yamamoto K

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama.

RESUMEN / SUMMARY: - BACKGROUND: Chronic infection with hepatitis C virus (HCV) decreases health-related quality of life (HRQOL). The present study was planned to investigate the impact of HRQOL of patients with chronic hepatitis C (CHC) on the outcomes of therapy with pegylated interferon and ribavirin, in addition to IL28B polymorphisms. METHODS: The present study enrolled 228 CHC patients, and assessed their HRQOLs prospectively with the 36-item short-form health survey. RESULTS: The patients with chronic hepatitis C have lower physical HRQOL status than the general population (P = 0.037, the Z test). The patients with advanced liver diseases exhibited further decreases in HRQOL (P = 0.036, Spearman's rank correlation coefficient). The score of total HRQOL was significantly lower in the group with sustained virological response (SVR) to the therapy with pegylated interferon and ribavirin than the non-SVR group (P = 0.031, the Mann-Whitney U test), with significantly lower scores of mental component and its comprising subscales in the SVR group. Stepwise multivariate logistic regression analysis showed that low HRQOL score \leq 400 points was significantly associated with SVR (odds ratio = 2.4, P = 0.013), independently from high platelet counts, low HCV RNA, favorable SNP type of IL28B, and HCV serotype 2. The patients with low HRQOL score will had significantly less decrease in HRQOL score by 4 weeks of the treatment than those with high HRQOL score at baseline (P = 0.0045). CONCLUSIONS: HRQOL is one of the significant predictor of the outcomes of therapy with pegylated interferon and ribavirin independently from IL28B polymorphism.

[440]

TÍTULO / TITLE: - Lepista sordida polysaccharide induces apoptosis of Hep-2 cancer cells via mitochondrial pathway.

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

REVISTA / JOURNAL: - Int J Biol Macromol. 2013 Jul 3;61C:97-101. doi: 10.1016/j.ijbiomac.2013.06.052.

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

[1016/j.ijbiomac.2013.06.052](#)

AUTORES / AUTHORS: - Miao S; Mao X; Pei R; Miao S; Xiang C; Lv Y; Yang X; Sun J; Jia S; Liu Y

INSTITUCIÓN / INSTITUTION: - Department of Head and Neck Surgery, The Third Affiliated Hospital of Harbin Medical University, Haping Road 150, 150081 Harbin, China.

RESUMEN / SUMMARY: - In our previous study, a potential antitumor polysaccharide (LSPc1) was screened from the fruiting bodies of *Lepista sordida*. However, its molecular mechanism of cell death induction on Hep-2 human laryngocarcinoma cells has still not been determined. The present study evaluated the anticancer efficacy and associated mechanisms of LSPc1 on Hep-2 cells in vitro. We found that LSPc1-induced inhibition of cell proliferation was associated with an increase in G2/M-phase arrest at 48h. Typical morphological and biochemical features of apoptosis were also observed in LSPc1-treated cells. Furthermore, LSPc1 led a loss of mitochondrial membrane potential ($\Delta\psi$), increased the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2, induced cytochrome c release, and increased the activity of caspase-3 and -9, which altogether account for apoptotic cell death. Taken together, our study suggests that intrinsic mitochondrial caspase dependent pathway plays a very important role in LSPc1-induced cancer apoptosis and these results provided strong experimental evidence for the use of LSPc1 as a potential therapeutic agent in cancer for laryngocarcinoma.

[441]

TÍTULO / TITLE: - Akebia saponin PA induces autophagic and apoptotic cell death in AGS human gastric cancer cells.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Jul 9;59C:703-708. doi: 10.1016/j.fct.2013.06.059.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.06.059](#)

AUTORES / AUTHORS: - Xu MY; Lee DH; Joo EJ; Son KH; Kim YS

INSTITUCIÓN / INSTITUTION: - Natural Products Research Institute, College of Pharmacy, Seoul National University, Seoul 151-742, Republic of Korea.

RESUMEN / SUMMARY: - In this study, we investigated the anticancer mechanism of akebia saponin PA (AS), a natural product isolated from *Dipsacus asperoides* in human gastric cancer cell lines. It was shown that AS-induced cell death is

caused by autophagy and apoptosis in AGS cells. The apoptosis-inducing effect of AS was characterized by annexin V/propidium (PI) staining, increase of sub-G1 phase and caspase-3 activation, while the autophagy-inducing effect was indicated by the formation of cytoplasmic vacuoles and microtubule-associated protein 1 light chain-3 II (LC3-II) conversion. The autophagy inhibitor bafilomycin A1 (BaF1) decreased AS-induced cell death and caspase-3 activation, but caspase-3 inhibitor Ac-DEVD-CHO did not affect LC3-II accumulation or AS-induced cell viability, suggesting that AS induces autophagic cell death and autophagy contributes to caspase-3-dependent apoptosis. Furthermore, AS activated p38/c-Jun N-terminal kinase (JNK), which could be inhibited by BaF1, and caspase-3 activation was attenuated by both SB202190 and SP600125, indicating that AS-induced autophagy promotes mitogen-activated protein kinases (MAPKs)-mediated apoptosis. Taken together, these results demonstrate that AS induces autophagic and apoptotic cell death and autophagy plays the main role in akebia saponin PA-induced cell death.

[442]

TÍTULO / TITLE: - Proteomic-based identification of multiple pathways underlying n-butylidenephthalide-induced apoptosis in LNCaP human prostate cancer cells.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Jun 12;59C:281-288. doi: 10.1016/j.fct.2013.05.045.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.05.045](#)

AUTORES / AUTHORS: - Pang CY; Chiu SC; Harn HJ; Zhai WJ; Lin SZ; Yang HH

INSTITUCIÓN / INSTITUTION: - Department of Medical Research, Buddhist Tzu Chi General Hospital, Hualien 970, Taiwan; Institute of Medical Sciences, Tzu Chi University, Hualien 970, Taiwan.

RESUMEN / SUMMARY: - Although numerous studies have shown the cancer-preventive properties of butylidenephthalide (BP), there is little report of BP affecting human prostate cancer cells. In the present study, proteomic-based approaches were used to elucidate the anticancer mechanism of BP in LNCaP human prostate cancer cells. BP treatment decreased the viability of LNCaP human prostate cancer cells in a concentration- and time-dependent manner, which was correlated with G0/G1 phase cell cycle arrest. Increased cell cycle arrest was associated with a decrease in the level of CCND1, CDK2, and PCNA proteins and an increase in the level of CDKN2A, CDKN1A, and SFN proteins. Proteomic studies revealed that among 48 differentially expressed proteins, 25 proteins were down-regulated and 23 proteins were up-regulated and these proteins fall into one large protein-protein interaction network. Among these proteins, FAS, AIFM1, BIK, CYCS, SFN, PPP2R1A, CALR, HSPA5, DDIT3, and ERN1 are apoptosis and endoplasmic reticulum (ER) stress

associated proteins. Proteomic data suggested that multiple signaling pathways including FAS-dependent pathway, mitochondrial pathway, and ER stress pathway are involved in the apoptosis induced by BP.

[443]

TÍTULO / TITLE: - Ki 67 is an Independent Predictive Biomarker of Cancer Specific and Local Recurrence-Free Survival After Lung Tumor Ablation.

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

REVISTA / JOURNAL: - Ann Surg Oncol. 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1245/s10434-013-3140-](#)

[1](#)

AUTORES / AUTHORS: - Sofocleous CT; Garg SK; Cohen P; Petre EN; Gonen M; Erinjeri JP; Downey RJ; Travis WD; Solomon SB

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, sofoclec@mskcc.org.

RESUMEN / SUMMARY: - BACKGROUND: The objective of this work was to evaluate the feasibility of histopathological analysis of tissue extracted on multitined electrodes and assess whether tissue characteristics can be used as biomarkers of oncologic outcomes after lung tumor radiofrequency (RF) ablation. METHODS: Treatment-related data regarding RF ablation of lung malignancies at our institution was collected using a Health Insurance Portability and Accountability Act-compliant ablation database. Institutional review board waiver was obtained for this study. Immunohistochemical analysis of tissue extracted from the electrodes after lung tumor RF ablation was performed for proliferation (Ki-67) and apoptosis (caspase-3). Patient, tumor demographics, and ablation parameters were recorded. Local tumor progression-free survival (LPFS), disease-specific survival (DSS), and overall survival (OS) were assessed using Kaplan-Meier methodology. Multivariate analysis determined factors affecting these oncological outcomes. RESULTS: A total of 47 lung tumors in 42 patients were ablated; 30 specimens were classified as coagulation necrosis (CN) and 17 as Ki-67-positive (+) tumor cells (viable). Tumor sizes were similar in the CN and Ki-67+ groups ($P = 0.32$). Median LPFS was 10 versus 16 months for Ki-67+ and CN groups, and 1-year LPFS was 34 and 75 %, respectively ($P = 0.003$). Median OS was 20 and 46 months ($P = 0.12$), and median DSS was 20 and 68 months ($P = 0.01$) for the Ki-67 + and CN groups, respectively. Identification of Ki-67+ tumor cells more than tripled the risk of death from cancer [hazard ratio (HR) = 3.65; 95 % confidence interval (95 % CI), 1.34-9.95; $P = 0.01$] and tripled the risk of local tumor progression (LTP) (HR = 3.01; 95 % CI, 1.39-6.49; $P = 0.005$). CONCLUSIONS: Ki-67+ tumor cells on the electrode after pulmonary tumor RF ablation is an independent predictor of LTP, shorter LPFS, and DSS.

[444]

TÍTULO / TITLE: - Adenovirus vector-mediated Gli1 siRNA induces growth inhibition and apoptosis in human pancreatic cancer with Smo-dependent or Smo-independent Hh pathway activation in vitro and in vivo.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jun 18. pii: S0304-3835(13)00460-6. doi: 10.1016/j.canlet.2013.06.010.

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

1016/j.canlet.2013.06.010

AUTORES / AUTHORS: - Guo J; Gao J; Li Z; Gong Y; Man X; Jin J; Wu H

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China.

RESUMEN / SUMMARY: - Activation of Hedgehog (Hh) signaling pathway is a core molecular mechanism in pancreatic carcinogenesis. However, the inhibition of upstream Hh signals does not inhibit the growth of a subset of pancreatic cancer (PC). This study was to examine the effect of siRNA targeting Gli1, the downstream component of Hh pathway, on PC cells and to provide some insight into the underlying mechanisms. A Gli1siRNA-expressing adenovirus (Ad-U6-Gli1siRNA) was constructed, and its effect on PC cells was investigated in vitro and in vivo. Gli1 was expressed in 83.3% (20/24) PC tissues, whereas no expression was found in normal pancreatic ductal epithelium. Gli1 was expressed in SW1990 and CFPAC cells in which Smo was completely absent, as well as in PaTu8988, Panc-1 and BxPC-3 cells in which Smo was concomitantly present. Ad-U6-Gli1siRNA induced cell growth inhibition, strong G0/G1 cell cycle arrest and apoptosis in all five human PC cell lines. Meanwhile, Ad-U6-Gli1siRNA significantly suppressed the expression of Gli1, Ptch1 and two target genes, Cyclin D2 and Bcl-2, in all five lines. Furthermore, two tumor xenograft nude mice models were established by subcutaneously injecting Smo-positive Panc-1 cells or Smo-negative SW1990 cells. The in vivo experimental results demonstrated that Ad-U6-Gli1siRNA inhibited the growth of both Panc1-derived and SW1990-derived tumors and induced cell apoptosis. Our study indicates that Gli1-targeting siRNA could induce growth inhibition and apoptosis in PC through knockdown of Gli1 and its target genes; and this method may represent a more effective therapeutic strategy for PC with Smo-dependent or Smo-independent Hh pathway activation.

[445]

TÍTULO / TITLE: - Parthenolide reverses doxorubicin resistance in human lung carcinoma A549 cells by attenuating NF-kappaB activation and HSP70 up-regulation.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Jun 20;221(2):73-82. doi: 10.1016/j.toxlet.2013.06.215.

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

[1016/j.toxlet.2013.06.215](http://dx.doi.org/10.1016/j.toxlet.2013.06.215)

AUTORES / AUTHORS: - Xin Y; Yin F; Qi S; Shen L; Xu Y; Luo L; Lan L; Yin Z

INSTITUCIÓN / INSTITUTION: - Jiangsu Province Key Laboratory for Molecular and Medical Biotechnology, College of Life Science, Nanjing Normal University, Nanjing 210023, Jiangsu, PR China.

RESUMEN / SUMMARY: - Chemotherapy resistance represents a major problem for the treatment of patients with lung carcinomas. Parthenolide (PN), a naturally occurring small molecule found in herb feverfew, has been used in clinical treatment. Although its importance in treating the chemotherapy resistance has been shown, the pharmacological benefits of PN for lung cancer with multidrug resistance are underappreciated. Using human lung epithelial carcinoma A549 and A549 derived DOX-resistant A549/DOX cell lines, we found that PN enhanced the apoptotic cytotoxicity of DOX in A549/DOX cells. PN inhibited P-glycoprotein (P-gp) up-regulation and promoted the intracellular accumulation of DOX in A549/DOX cells. PN also exhibited inhibitory effect on NF-kappaB activation in A549/DOX cells, suggesting that inhibition of NF-kappaB was involved in attenuating P-gp expression by PN. Moreover, we found that PN could also effectively inhibit the HSP70 up-regulation in A549/DOX cells. Further studies revealed a positive correlation between HSP70 and P-gp expression. Overexpression of HSP70 upregulated P-gp expression independently of NF-kappaB activation in A549 cells, and knockdown of HSP70 caused a reduced expression of P-gp in A549/DOX cells. RT-PCR experiments showed that HSP70 modulated the P-gp expression mainly at transcription level. Taken together, PN can reverse DOX resistance through suppressing P-gp expression by mechanisms involving attenuation of NF-kappaB activation and HSP70 up-regulation. Our results not only provide insight into potential use of PN in reversing P-gp mediated MDR to facilitate lung cancer chemotherapy, but also highlight a potential role of HSP70 in the development of drug resistance.

[446]

TÍTULO / TITLE: - ALK amplification and protein expression predict inferior prognosis in neuroblastomas.

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

REVISTA / JOURNAL: - Exp Mol Pathol. 2013 Jun 21;95(2):124-130. doi: 10.1016/j.yexmp.2013.06.002.

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

[1016/j.yexmp.2013.06.002](http://dx.doi.org/10.1016/j.yexmp.2013.06.002)

AUTORES / AUTHORS: - Wang M; Zhou C; Sun Q; Cai R; Li Y; Wang D; Gong L

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Basic Medical College, Capital Medical University, Beijing, China.

RESUMEN / SUMMARY: - BACKGROUND: ALK gene has been identified as a major neuroblastoma (NBL) predisposition gene. But ALK gene copy number and protein expression in ganglioneuroblastoma (GNBL) and ganglioneuroma (GN) are poorly described in the literature. Furthermore, there are controversies on the correlation between ALK protein expression and clinical outcome in NBL. METHODS: We evaluated MYCN/ALK gene copy number by fluorescence in situ hybridization (FISH) and detected ALK protein expression by immunohistochemistry (IHC) in 188 NBL, 52 GNBL and 6 GN samples and analyzed their association with clinical outcome of the patients. RESULTS: Although ALK gene copy number increase is a recurrent genetic aberration of neuroblastic tumors (NTs) (39.1%, 96/246), ALK amplification was only present in three NBLs (1.2%, 3/246). The frequency of ALK positivity in NBL (50.5%, 51/101) was significantly higher than in GNBL (22.6%, 7/31) and in GN (0.0%, 0/4) ($P < 0.05$). In addition, ALK positivity also significantly correlates with MYCN/ALK gene copy number increases ($P < 0.05$). Kaplan-Meier survival analysis indicated that MYCN/ALK amplification is correlated with decreased overall survival in NBL. A better prognosis trend was observed in patients with MYCN/ALK gain tumors compared with those with MYCN/ALK normal tumors. Furthermore, ALK positivity significantly correlated with inferior survival in NBL ($P = 0.044$). CONCLUSION: ALK positivity in NTs correlated with advanced tumor types and MYCN/ALK gene copy number increases. ALK positivity predicts inferior prognosis in NBL and IHC is a simplified strategy to screen ALK positivity in clinical practice.

[447]

TÍTULO / TITLE: - Zinc at sub-cytotoxic concentrations induces heme oxygenase-1 expression in human cancer cells.

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

REVISTA / JOURNAL: - Cell Physiol Biochem. 2013;32(1):100-10. doi: 10.1159/000350128. Epub 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1159/000350128](#)

AUTORES / AUTHORS: - Xue J; Wang S; Wu J; Hannafon BN; Ding WQ

INSTITUCIÓN / INSTITUTION: - School of Radiation Medicine and Protection, Soochow University, Suzhou, P. R. China.

RESUMEN / SUMMARY: - Background/Aims: This study investigated the effects of zinc on heme oxygenase-1 (HO-1) expression in human cancer cells. Methods/Results: Zinc at sub-cytotoxic concentrations (50-100 μ M) induces HO-1 expression in the MDA-MB-231 (human breast cancer) and A2780 (human ovarian cancer) cell lines in a concentration- and time-dependent manner. The induction of HO-1 by zinc was detected after 4-6 hours of treatment, reached maximal level at 8 hours, and declined thereafter. Using a

human HO-1 gene promoter reporter construct, we identified two antioxidant response elements (AREs) that mediated the zinc-induced increase in HO-1 gene transcription, indicating that the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathway is involved in this event. This assumption was supported by the observations that knockdown of Nrf2 expression compromised the zinc-induced increase in HO-1 gene transcription, and that zinc increased Nrf2 protein expression and the Nrf2 binding to the AREs. Additionally, we found that the zinc-induced HO-1 gene transcription can be enhanced by clioquinol, a zinc ionophore, and reversed by pretreatment with TPEN, a known zinc chelator, indicating that an increase in intracellular zinc levels is responsible for this induction. Conclusion: These findings demonstrate that zinc at sub-cytotoxic concentrations induces HO-1 expression in human cancer cells. The biological significance of this induction merits further investigation.

[448]

TÍTULO / TITLE: - Tissue metabolite profiling identifies differentiating and prognostic biomarkers for prostate carcinoma.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jun 4. doi: 10.1002/ijc.28303.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28303](#)

AUTORES / AUTHORS: - Jung K; Reszka R; Kamlage B; Bethan B; Stephan C; Lein M; Kristiansen G

INSTITUCIÓN / INSTITUTION: - Department of Urology, University Hospital Charite, Schumannstrass 20/21, 10117 Berlin, Germany; Berlin Institute for Urologic Research, Schumannstrasse 20/21, 10117 Berlin, Germany.

RESUMEN / SUMMARY: - Metabolomic research offers a deeper insight into biochemical changes in cancer metabolism and is a promising tool for identifying novel biomarkers. We aimed to evaluate the diagnostic and prognostic potential of metabolites in prostate cancer (PCa) tissue after radical prostatectomy. In matched malignant and nonmalignant prostatectomy samples from 95 PCa patients, amino adipic acid, cerebronic acid, gluconic acid, glycerophosphoethanolamine, 2-hydroxybehenic acid, isopentenyl pyrophosphate, maltotriose, 7-methylguanine and tricosanoic acid were determined within a global metabolite profiling study using gas chromatography/liquid chromatography-mass spectrometry. The data were related to clinicopathological variables like prostate volume, tumor stage, Gleason score, preoperative prostate-specific antigen and disease recurrence in the follow-up. All nine metabolites showed higher concentrations in malignant than in nonmalignant samples except for gluconic acid and maltotriose, which had lower levels in tumors. Receiver-operating characteristics analysis demonstrated a significant discrimination for all metabolites between malignant and nonmalignant tissue with a maximal area under the curve of 0.86 for tricosanoic acid, whereas no correlation was observed between the metabolite

levels and the Gleason score or tumor stage except for gluconic acid. Univariate Cox regression and Kaplan-Meier analyses showed that levels of amino adipic acid, gluconic acid and maltotriose were associated with the biochemical tumor recurrence (prostate-specific antigen > 0.2 ng/mL). In multivariate Cox regression analyses, amino adipic acid together with tumor stage and Gleason score remained in a model as independent marker for prediction of biochemical recurrence. This study proved that metabolites in PCa tissue can be used, in combination with traditional clinicopathological factors, as promising diagnostic and prognostic tools.

[449]

TÍTULO / TITLE: - Overexpression of CDC28 protein kinase regulatory subunit 1B confers an independent prognostic factor in nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - APMIS. 2013 Jul 24. doi: 10.1111/apm.12136.

●● [Enlace al texto completo \(gratis o de pago\) 1111/apm.12136](#)

AUTORES / AUTHORS: - Lee SW; Lin CY; Tian YF; Sun DP; Lin LC; Chen LT; Hsing CH; Huang CT; Hsu HP; Huang HY; Wu LC; Li CF; Shiue YL

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Chi-Mei Medical Center, Tainan, Taiwan.

RESUMEN / SUMMARY: - Data mining on public domain identified that CDC28 protein kinase regulatory subunit 1B (CKS1B) transcript was highly expressed in nasopharyngeal carcinoma (NPC). The expression of CKS1B protein and its clinicopathological associations in patients with NPC were further evaluated. Immunoexpression of CKS1B was retrospectively assessed in biopsies of 124 consecutive NPC patients without initial distant metastasis and treated with consistent guidelines. The correlations between CKS1B immunoexpression levels and clinicopathological features, as well as patient survivals, were analyzed. High CKS1B expression (49.2%) was correlated with the 7th American Joint Committee on Cancer (AJCC) stage ($p = 0.014$). In multivariate analyses, high CKS1B expression emerged as an independent prognostic factor for worse disease-specific survival ($p < 0.001$), metastasis-free survival ($p < 0.001$), and local recurrence-free survival ($p = 0.001$). High expression of CKS1B is common and associated with adverse prognostic factors and might confer tumor aggressiveness through dysregulation of the cyclin-dependent protein kinase (intrinsic regulatory activity) during cell cycle progression.

[450]

TÍTULO / TITLE: - Lymphoma and myeloma cells are highly sensitive to growth arrest and apoptosis induced by artesunate.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Jul 22. doi: 10.1111/ejh.12176.

●● Enlace al texto completo (gratis o de pago) 1111/ejh.12176

AUTORES / AUTHORS: - Holien T; Olsen OE; Misund K; Hella H; Waage A; Ro TB; Sundan A

INSTITUCIÓN / INSTITUTION: - KG Jebsen Center for Myeloma Research and Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

RESUMEN / SUMMARY: - **OBJECTIVES:** The use of new drugs has improved the treatment of multiple myeloma and diffuse large B-cell lymphoma (DLBCL). Nevertheless, over time many patients relapse and develop resistance to treatment, and efforts are needed to overcome drug resistance. The widely used malaria drug artesunate has been reported to have anti-tumor activity and we aimed to test the effects of artesunate on a panel of myeloma and lymphoma cells. **METHODS:** Myeloma and DLBCL cell lines were treated with artesunate in vitro. The effects of artesunate treatment were evaluated using ATP-content measurements for proliferation and annexin V/propidium iodide labeling for apoptosis. Western blotting was used to look for artesunate-induced protein changes. In addition we measured artesunate effects on patient myeloma cells in the presence of bone marrow stromal cells. **RESULTS:** Artesunate treatment efficiently inhibited cell growth and induced apoptosis in cell lines. Apoptosis was induced concomitantly with downregulation of MYC and anti-apoptotic Bcl-2 family proteins, as well as with cleavage of caspase-3. The IC₅₀ values of artesunate in cell lines varied between 0.3 and 16.6 μM. Furthermore, some primary myeloma cells were also sensitive to artesunate at doses around 10 μM. Concentrations of this order are pharmacologically relevant as they can be obtained in plasma after intravenous administration of artesunate for malaria treatment. **CONCLUSION:** Our findings indicate that artesunate is a potential drug for treatment of multiple myeloma and diffuse large B-cell lymphoma at doses of the same order as currently in use for treatment of malaria without serious adverse effects. This article is protected by copyright. All rights reserved.

[451]

TÍTULO / TITLE: - Berberine induces apoptosis via the mitochondrial pathway in liver cancer cells.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 19. doi: 10.3892/or.2013.2543.

●● Enlace al texto completo (gratis o de pago) 3892/or.2013.2543

AUTORES / AUTHORS: - Yip NK; Ho WS

INSTITUCIÓN / INSTITUTION: - School of Life Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, P.R. China.

RESUMEN / SUMMARY: - Current chemotherapeutic strategies for liver cancer have limitations. Thus, the demand for complementary medicine is warranted. We evaluated the antitumor potential of berberine, a naturally bioactive

phytochemical from *Coptis chinensis* Franch against Huh7 cancer cells and WRL68 liver cells. The antitumor activity of berberine was evaluated by flow cytometry. The caspase-dependent pathway was assessed using western blot analysis. Results showed that berberine induced the apoptosis of liver cancer cells through procaspase-9, and its effector caspases, procaspase-3 and procaspase-7. Flow cytometry revealed that berberine caused cell cycle arrest at the M/G1 phase. The results of reverse transcription-polymerase chain reaction showed that berberine increased the expression of Bax, which resulted in the activation of the caspase cascade. The present findings demonstrated that berberine induces the apoptosis of Huh7 cells via the mitochondrial pathway.

[452]

TÍTULO / TITLE: - Histone deacetylase inhibitors as potential therapeutic approaches for chordoma: An immunohistochemical and functional analysis.

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

REVISTA / JOURNAL: - J Orthop Res. 2013 Jul 24. doi: 10.1002/jor.22447.

●● [Enlace al texto completo \(gratis o de pago\) 1002/jor.22447](#)

AUTORES / AUTHORS: - Susanne S; Birgit L; Beate R; Verena FE; Alfred B; Franz Q; Aron L; Pal VP; Johannes H; Andreas L; Bernadette L

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedics and Orthopaedic Surgery, Medical University of Graz, Auenbruggerplatz 5, 8036, Graz, Austria.

RESUMEN / SUMMARY: - Chordomas are rare malignancies of the axial skeleton. Therapy is mainly restricted to surgery. This study investigates histone deacetylase (HDAC) inhibitors as potential therapeutics for chordomas. Immunohistochemistry (IHC) was performed using the HDAC 1-6 antibodies on 50 chordoma samples (34 primary tumors, 16 recurrences) from 44 patients (27 male, 17 female). Pan-HDAC-inhibitors Vorinostat (SAHA), Panobinostat (LBH-589), and Belinostat (PXD101) were tested for their efficacy in the chordoma cell line MUG-Chor1 via Western blot, cell cycle analysis, caspase 3/7 activity (MUG-Chor1, UCh-1), cleaved caspase-3, and PARP cleavage. p-Values below 0.05 were considered significant. IHC was negative for HDAC1, positive for HDAC2 in most (n = 36; 72%), and for HDACs 3-6 in all specimens available (n = 43; 86%). HDAC6 expression was strongest. SAHA and LBH-589, but not PXD101 caused a significant increase of G2/M phase cells and of cleaved caspase-3 (p = 0.0003, and p = 0.0014 after 72 h, respectively), and a peak of caspase 3/7 activity. PARP cleavage confirmed apoptosis. The presented chordoma series expressed HDACs 2-6 with strongest expression of HDAC6. SAHA and LBH-589 significantly increased apoptosis and changed cell cycle distribution in vitro. HDAC-inhibitors should be further evaluated as therapeutic options for chordoma. © 2013 Orthopaedic Research Society Published by Wiley Periodicals, Inc. J Orthop Res 9999:1-7, 2013.

[453]

TÍTULO / TITLE: - In vitro antioxidant and antiproliferative effects of ellagic acid and its colonic metabolite, urolithins, on human bladder cancer T24 cells.

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

REVISTA / JOURNAL: - Food Chem Toxicol. 2013 Jun 26;59C:428-437. doi: 10.1016/j.fct.2013.06.025.

●● Enlace al texto completo (gratis o de pago) [1016/j.fct.2013.06.025](#)

AUTORES / AUTHORS: - Qiu Z; Zhou B; Jin L; Yu H; Liu L; Liu Y; Qin C; Xie S; Zhu F

INSTITUCIÓN / INSTITUTION: - Department of Medical Microbiology, School of Medicine, Wuhan University, No. 185 Donghu Road, Wuhan 430071, People's Republic of China.

RESUMEN / SUMMARY: - Urolithins were the metabolites of ellagic acid by intestinal flora in gastrointestinal tract. In previous research, it was found that urolithins could mainly inhibit prostate cancer and colon cancer cell growth. However, there is no report about bladder cancer therapy of urolithins. In this paper, three urolithin-type compounds (urolithin A, urolithin B, 8-OMe-urolithin A) and ellagic acid were evaluated for antiproliferative activity in vitro against human bladder cancer cell lines T24. The IC50 values for T24 cell inhibition were 43.9, 35.2, 46.3 and 33.7 μM for urolithin A, urolithin B, 8-OMe-urolithin A and ellagic acid, respectively. After the administration of urolithins and ellagic acid, we found these compounds could increase mRNA and protein expression of Phospho-p38 MAPK, and decrease mRNA and protein expression of MEKK1 and Phospho-c-Jun in T24 cells. Caspase-3 was also activated and PPAR-γ protein expression increased in drug-induced apoptosis. And what's more, the antioxidant assay afforded by three urolithins and EA treatments were associated with decreases in the intracellular ROS and MDA levels, and increased SOD activity in H₂O₂-treated T24 cells. The results suggested that these compounds could inhibit cell proliferation by p38-MAPK and/or c-Jun mediated caspase-3 activation and reduce the oxidative stress status in bladder cancer.

[454]

TÍTULO / TITLE: - RhoB Promotes Cancer Initiation by Protecting Keratinocytes from UVB-Induced Apoptosis but Limits Tumor Aggressiveness.

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

REVISTA / JOURNAL: - J Invest Dermatol. 2013 Jun 21. doi: 10.1038/jid.2013.278.

●● Enlace al texto completo (gratis o de pago) [1038/jid.2013.278](#)

AUTORES / AUTHORS: - Meyer N; Peyret-Lacombe A; Canguilhem B; Medale-Giamarchi C; Mamouni K; Cristini A; Monferran S; Lamant L; Filleron T; Pradines A; Sordet O; Favre G

INSTITUCIÓN / INSTITUTION: - 1] Inserm, UMR 1037-CRCT, Toulouse, France [2] Université Paul Sabatier, Toulouse, France [3] Department of Dermatology, Hôpital Larrey, Toulouse, France.

RESUMEN / SUMMARY: - The role of UVB-induced apoptosis in the formation of squamous cell carcinoma (SCC) is recognized. We previously identified the small RhoB (Ras homolog gene family, member B) GTPase, an early response gene to cellular stress, as a critical protein controlling apoptosis of human keratinocytes after UVB exposure. Here we generated SKH1 (hairless immunocompetent mouse) mice invalidated for RhoB to evaluate its role in UVB-induced skin carcinogenesis in vivo. We show that *rhob*^{-/-} mice have a lower risk of developing UVB-induced keratotic tumors and actinic keratosis that is associated with a higher sensitivity of UVB-exposed keratinocytes to apoptosis. We extend this observation to primary cultures of normal human keratinocytes in which RhoB was downregulated with small interfering RNA (siRNA) and further show that the hypersensitivity to apoptosis depends on B-cell lymphoma 2 (Bcl-2) downregulation. In *rhob*^{-/-} mice, the UVB-induced tumors were preferentially undifferentiated and highly proliferative. Finally, we show in humans an almost constant loss of RhoB expression in undifferentiated SCCs. These undifferentiated and RhoB-deficient tumors have elevated phosphorylated histone H2AX (gammaH2AX) and 53BP1, two markers of DNA double-strand breaks. Together, our results indicate that UVB-induced RhoB expression participates in in vivo SCC initiation by increasing keratinocyte survival. Conversely, RhoB may limit tumor aggressiveness as loss of RhoB expression in tumor cells is associated with tumor progression. *Journal of Investigative Dermatology* advance online publication, 18 July 2013; doi:10.1038/jid.2013.278.

[455]

TÍTULO / TITLE: - Prognostic significance of mammalian sterile 20-like kinase 1 in breast cancer.

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

REVISTA / JOURNAL: - *Tumour Biol.* 2013 Jun 6.

- [Enlace al texto completo \(gratuito o de pago\) 1007/s13277-013-0895-](#)

[8](#)

AUTORES / AUTHORS: - Lin X; Cai F; Li X; Kong X; Xu C; Zuo X; Yang Q

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Qilu Hospital, Shandong University, Jinan, 250012, Shandong, China, linxy077@gmail.com.

RESUMEN / SUMMARY: - Mammalian sterile 20-like kinase 1 (Mst1) has been proved in the process of apoptosis and tumor suppression. The aim of the study was to investigate the expression of Mst1 in breast cancer and to evaluate its prognostic significance. The expression of Mst1 was examined in 110 breast cancer patients by immunohistochemistry, in which 80 (72.7 %) were defined as positive for Mst1 expression. Patients with negative expression of Mst1 had

poor overall survival, comparing with those with positive expression using Kaplan-Meier survival analysis (P = 0.009). Multivariate analysis using Cox proportional hazards model showed that Mst1 expression was a significant independent prognostic factor in breast cancer (P = 0.030). Our results presented the tumor suppressive role of Mst1, and confirmed Mst1 was a prognostic factor in human breast cancer.

[456]

TÍTULO / TITLE: - Quercetin potentiates apoptosis by inhibiting nuclear factor-kappaB signaling in H460 lung cancer cells.

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

REVISTA / JOURNAL: - Biol Pharm Bull. 2013;36(6):944-51.

AUTORES / AUTHORS: - Youn H; Jeong JC; Jeong YS; Kim EJ; Um SJ

INSTITUCIÓN / INSTITUTION: - Department of Bioscience and Biotechnology, BK21 Graduate Program, Sejong University, Seoul, Korea.

RESUMEN / SUMMARY: - The herbal flavonoid quercetin inhibits the growth of various cancer cells, but how it affects human cancer cells, particularly lung cancer cells, is unclear. We investigated the anticancer activity of quercetin and the underlying molecular mechanisms in non-small cell lung cancer (NSCLC) cells. Quercetin strongly inhibited cell proliferation, and increased sub-G1 and apoptotic cell populations regardless of p53 status. Quercetin-induced apoptosis was verified by caspase cleavage, Hoechst staining, trypan blue exclusion, and DNA fragmentation assays. Microarray analysis using H460 cells indicated that quercetin increased the expression of genes associated with death receptor signaling tumor necrosis factor-related apoptosis-inducing ligand receptor (TRAILR), caspase-10, interleukin (IL) 1R DNA fragmentation factor 45 (DFF45), tumor necrosis factor receptor (TNFR) 1, FAS, inhibitor of kappaB (IkappaB) and cell cycle inhibition growth arrest and DNA-damage inducible 45 (GADD45), p21(Cip1)), but decreased the expression of genes involved in nuclear factor (NF)-kappaB activation (NF-kappaB, IKKalpha). Further validation assays confirmed that quercetin inhibited growth by suppressing NF-kappaB and by increasing the expression of death receptors and cell cycle inhibitors. Taken together, these findings suggest that quercetin may be useful in the prevention and therapy of NSCLC.

[457]

TÍTULO / TITLE: - Impact of effective tumor necrosis factor-alfa inhibitor treatment on arterial intima-media thickness in psoriasis: Results of a pilot study.

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

REVISTA / JOURNAL: - J Am Acad Dermatol. 2013 Jul 23. pii: S0190-9622(13)00647-6. doi: 10.1016/j.jaad.2013.06.019.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.jaad.2013.06.019](#)

AUTORES / AUTHORS: - Jokai H; Szakonyi J; Kontar O; Marschalko M; Szalai K; Karpati S; Hollo P

INSTITUCIÓN / INSTITUTION: - Department of Dermatovenerology and Oncodermatology, Semmelweis University, Budapest, Hungary. Electronic address: jokaihajnalka@gmail.com.

RESUMEN / SUMMARY: - **BACKGROUND:** Psoriasis is associated with higher incidence of atherosclerotic comorbidities. Sustained arterial wall inflammation mediated by common cytokines of psoriasis and atherogenesis precedes atherosclerotic plaque development. Increased intima-media thickness (IMT) is an accepted indicator of subclinical atherosclerosis and has been reported in severe psoriasis. **OBJECTIVE:** This pilot study aimed to clarify whether effective long-term tumor necrosis factor- α inhibition decreases IMT in psoriasis. **METHODS:** In 16 patients with severe psoriasis, the Psoriasis Area and Severity Index score was calculated before therapy (etanercept, infliximab, adalimumab) and after 6-month treatment. Simultaneously, carotid and brachial IMT was measured by high-resolution, B-mode ultrasonography. Difference between initial and 6-month IMT values was determined for monitored arteries collectively and separately in carotid and brachial arteries. **RESULTS:** All of 16 patients achieved Psoriasis Area and Severity Index 75, and 14 of 16 achieved Psoriasis Area and Severity Index 90 improvement. In the group of patients without initial calcified atherosclerotic plaques (13 of 16) significant IMT decrease was detected when arteries were measured collectively ($P = .0002$). Initial and follow-up data differed significantly also at individual analysis of carotid ($P = .011$) and brachial ($P = .006$) arteries. Eleven of 13 patients had initial carotid IMT exceeding age-adjusted normal values. The other group (3 of 16) with initial manifest plaques showed increasing IMT tendency. Their baseline ultrasonography revealed carotid IMT above the upper limit of healthy adults' age-adjusted values. **LIMITATIONS:** Study limitation involves small patient numbers, self-controlled study design, and lack of patients' stratification according to common cardiovascular risk factors. **CONCLUSION:** In our pilot study effective tumor necrosis factor- α inhibition was found to decrease IMT in psoriatic patients without irreversible atherosclerotic plaques. Further analysis is recommended to confirm and complete our primary observations.

[458]

TÍTULO / TITLE: - LDK378: A Promising Anaplastic Lymphoma Kinase (ALK) Inhibitor.

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

REVISTA / JOURNAL: - J Med Chem. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) 1021/jm401005u

AUTORES / AUTHORS: - Chen J; Jiang C; Wang S

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, University of Michigan Comprehensive Cancer Center, University of Michigan , Ann Arbor, Michigan 48109, United States.

[459]

TÍTULO / TITLE: - Overexpression of thymidylate synthetase confers an independent prognostic indicator in nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - Exp Mol Pathol. 2013 Aug;95(1):83-90. doi: 10.1016/j.yexmp.2013.05.006. Epub 2013 May 28.

- Enlace al texto completo (gratis o de pago)

[1016/j.yexmp.2013.05.006](#)

AUTORES / AUTHORS: - Lee SW; Chen TJ; Lin LC; Li CF; Chen LT; Hsing CH; Hsu HP; Tsai CJ; Huang HY; Shiue YL

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Chi-Mei Medical Center, Liouying, Tainan, Taiwan.

RESUMEN / SUMMARY: - Data mining on public domain identified that thymidylate synthetase (TYMS) and dihydrofolate reductase (DHFR) transcripts were significantly higher expressed in nasopharyngeal carcinoma (NPC). In the folate pathway, TYMS catalyzes the methylation of deoxyuridylate to deoxythymidylate using 5,10-methylenetetrahydrofolate [5,10-CH₂=THF, derived from tetrahydrofolate (THF)], as a cofactor. This function maintains the thymidine-5-prime monophosphate pool critical for DNA replication and repair and, THF is generated from dihydrofolate (DHF) through the activity of DHFR. Immunoexpression of TYMS and DHFR were retrospectively assessed in biopsies of 124 consecutive NPC patients without initial distant metastasis and treated with consistent guidelines. The outcome was correlated with clinicopathological features and patient survivals. Results indicated that high TYMS (50%) expressions were correlated with primary tumor (p=0.008) and AJCC stage (p=0.006), and high DHFR (50%) expression were correlated with nodal status (p=0.039) and AJCC stage (p=0.029) (7th American Joint Committee on Cancer), respectively. In multivariate analyses, high TYMS expression emerged as an independent prognosticator for worse disease-specific survival (p<0.001), distal metastasis-free survival (p=0.002) and local recurrence-free survival (p<0.001), along with AJCC stage. Therefore, TYMS expression is common and associated with adverse prognosticators and might confer tumor aggressiveness through dysregulation of the nucleotide biosynthetic process.

TÍTULO / TITLE: - Activation of Rac1 GTPase promotes leukemia cell chemotherapy resistance, quiescence and niche interaction.

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

REVISTA / JOURNAL: - Mol Oncol. 2013 May 15. pii: S1574-7891(13)00080-X. doi: 10.1016/j.molonc.2013.05.001.

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

1016/j.molonc.2013.05.001

AUTORES / AUTHORS: - Wang JY; Yu P; Chen S; Xing H; Chen Y; Wang M; Tang K; Tian Z; Rao Q; Wang J

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, PR China.

RESUMEN / SUMMARY: - Leukemia stem cells (LSCs) reside in bone marrow niche and receive important signals from the microenvironment that support self-renewal, maintain quiescence and endow LSC with the ability of chemotherapy resistance. Rac1 belongs to the small GTP-binding protein superfamily and is implicated in the interactions of hematopoietic progenitors and bone marrow niche. Our previous studies have shown that Rac1 is over-expressed in leukemia patients and activation of Rac1 GTPase is closely associated with the efficient migration of leukemia cells. However, the potential functions for Rac1 GTPase in LSCs behaviors and in the residence of leukemia cells in niche remain unknown. In this study, by forced expression of a dominant-negative form of Rac1 GTPase in a CD34+ myeloid leukemia cell line, as well as bone marrow cells from leukemia patients, we show that inactivation of Rac1 GTPase causes impaired migration and enhances chemotherapeutic sensitivity. Inactivation of Rac1 in leukemia cells also lead to a reduction in the frequency of cells in quiescent state and inhibition of homing to bone marrow niche. Gene expression analysis shows that inactivation of Rac1 down-regulates the expression of several cell intrinsic cell cycle inhibitors such as p21, p27, and p57, as well as the extrinsic molecules that mediated the interaction of LSC with osteoblastic niche. Furthermore, we show that Rac1 mediated the localization in niche is further attributed to the maintenance of quiescence. Our results provide evidence for the critical role of Rac1 GTPase in leukemia cell chemotherapy resistance, quiescence maintenance and the interaction with bone marrow microenvironment.

[460]

TÍTULO / TITLE: - 15,16-Dihydroanthraquinone I-induced Apoptosis in Human Colorectal Cancer Cells: Involvement of ATF3.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3225-31.

AUTORES / AUTHORS: - Suk FM; Jou WJ; Lin RJ; Lin SY; Tzeng FY; Liang YC

INSTITUCIÓN / INSTITUTION: - School of Medical Laboratory Science and Biotechnology, College of Medical Science and Technology, Taipei Medical University, 250 Wuxing St., Taipei 11031, Taiwan, R.O.C. ycliang@tmu.edu.tw.

RESUMEN / SUMMARY: - 15,16-Dihydrotanshinone I (DHTS) is a component of the traditional Chinese medicinal plant *Salvia miltiorrhiza* Bunge. In this study, DHTS at as low as 2.5 µg/ml concentration significantly inhibited proliferation of human benign (SW480) and malignant (SW620) colorectal cancer cells, as shown by 3-(4,5)-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide (MTT) and flow cytometric analysis. Activating transcription factor (ATF)-3, a basic leucine zipper-type transcription factor, was found to be predominantly up-regulated in DHTS-treated SW480 and SW620 cells. The up-regulation of ATF3 was blocked by a c-JUN N-terminal kinase (JNK) or p38 inhibitor. Overexpression of ATF3 resulted in a significant augmentation of DHTS-induced apoptosis of SW480 cells, but resistance to DHTS-induced apoptosis of SW620 cells. These results suggest that DHTS has a strong therapeutic or preventive potential against cancer. In addition, ATF3 has a dual role in DHTS-induced apoptosis, depending on the degree of malignancy of colorectal cancer.

[461]

TÍTULO / TITLE: - Individualised proteome profiling of human endometrial tumours improves detection of new prognostic markers.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Aug 6;109(3):704-13. doi: 10.1038/bjc.2013.359. Epub 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.359](http://dx.doi.org/10.1038/bjc.2013.359)

AUTORES / AUTHORS: - Attarha S; Andersson S; Mints M; Souchelnytskyi S
INSTITUCIÓN / INSTITUTION: - [1] Department of Oncology-Pathology, Karolinska Institutet, Z5:01, KS, Solna, 17176 Stockholm, Sweden [2] Department of Women's and Children's Health, Karolinska Institutet, KS, Solna, 17176 Stockholm, Sweden.

RESUMEN / SUMMARY: - Background: The individual features of tumours are often disregarded in cohort studies. As these features may represent a source for individualised cancer treatment, it is important to develop a novel approach for their assessment. Methods: We used proteomics, systems biology, and immunohistochemistry to explore protein expression in human endometrial tumours, to identify deregulated regulatory mechanisms, and to validate observed changes in protein expression using tissue microarrays. Results: Compared with the evaluation of common tumour features, the evaluation of individual tumour features gave a more comprehensive and detailed overview of the regulatory processes in endometrial tumours. Systemic analysis of the individual proteome profiles showed that endometrial tumours employed different proteins to regulate similar functions. Comparison of our data with publicly available data sets of molecular profiling of human endometrial tumours confirmed that individual tumour features are not simply irrelevant individual variations, but are indeed important in endometrial tumorigenesis. Validation through tissue microarray investigation of MST1 and

PKN1 proteins confirmed the usefulness of this approach, and suggested that MST1 and PKN1 may be considered as predictive biomarkers of endometrial cancer. Conclusion: We show that individualised profiling of endometrial tumours may deliver better insights into a tumour's physiology, thereby giving a better prediction of tumour development. Individual tumour features may also be used to tailor cancer treatment.

[462]

TÍTULO / TITLE: - New 5-aryl-1H-imidazoles display in vitro antitumor activity against apoptosis-resistant cancer models, including melanomas, through mitochondrial targeting.

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

REVISTA / JOURNAL: - J Med Chem. 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [1021/jm400287v](#)

AUTORES / AUTHORS: - Mathieu V; Van Den Berge E; Ceusters J; Konopka T; Cops A; Bruyere C; Pirker C; Berger W; Trieu-Van T; Serteyn D; Kiss R; Robiette R

RESUMEN / SUMMARY: - We designed and synthesized 48 aryl-1H-imidazole derivatives and investigated their in vitro growth inhibitory activity in cancer cell lines known to present various levels of resistance to pro-apoptotic stimuli. The IC50 in vitro growth inhibitory concentration of these compounds ranged from >100µM to single digit µM. Among the most active compounds, 2i displayed similar in vitro growth inhibition in cancer cells independently of the cells' levels of resistance to pro-apoptotic stimuli, and was found to be cytostatic in melanoma cell lines. Compound 2i was then tested by the National Cancer Institute Human Tumor Cell Line Anti-Cancer Drug Screen, and the NCI COMPARE algorithm did not reveal any correlation between its growth inhibition profiles with the NCI database compound profiles. The use of transcriptomically characterized melanoma models then enabled us to highlight mitochondrial targeting by 2i. This hypothesis was further confirmed by reactive oxygen production measurement and oxygen consumption analysis.

[463]

TÍTULO / TITLE: - Expression of DJ-1 in Endometrial Cancer: Close Correlation With Clinicopathological Features and Apoptosis.

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

REVISTA / JOURNAL: - Int J Gynecol Cancer. 2013 Jul;23(6):1029-35. doi: 10.1097/IGC.0b013e3182959182.

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

[1097/IGC.0b013e3182959182](#)

AUTORES / AUTHORS: - Shu K; Xiao Z; Long S; Yan J; Yu X; Zhu Q; Mei T

INSTITUCIÓN / INSTITUTION: - *Department of Gynecological Oncology, and daggerDepartment of Pathology, Jiangxi Maternity and Child Healthcare Hospital, No. 381 Ba-yi Rd, Nanchang City 330006, Jiangxi, PR China.

RESUMEN / SUMMARY: - OBJECTIVES: DJ-1 was originally cloned as a putative oncogene capable of transforming NIH3T3 cells in cooperation with H-Ras or c-Myc, which has been implicated in the pathogenesis of some solid tumors. The aim of this study was to investigate the expression and clinical significance of DJ-1 in endometrial cancer and study its effect on cell proliferation and apoptosis in endometrial cancer Ishikawa cells. METHODS: Reverse transcription polymerase chain reaction and Western blotting were performed to determine the DJ-1 expression in 100 surgical specimens of endometrial cancer tissues, paired tumor-adjacent tissues, and 30 surgical specimens of normal endometrium tissues. The proliferation variety of endometrial cancer Ishikawa cells was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium assay after transfecting the interference plasmid pGPU6/GFP/neo-DJ-1-shRNA into Ishikawa cells. Real-time polymerase chain reaction and Western blotting were used to evaluate the effect of interference plasmid on target gene expression. Apoptosis rate was determined by flow cytometry. RESULTS: DJ-1 expression in endometrial cancer tissues was higher than in tumor-adjacent tissues and normal endometrial tissues. At the same time, it was associated with signs of cancer progression, including differentiation, myometrial invasion depth, and presence of lymph node metastasis. Knocking down DJ-1 promoted the apoptosis of Ishikawa cells. CONCLUSIONS: High DJ-1 expression seems to be negatively correlated with apoptosis. Meanwhile, it may be part of the mechanisms for the development, invasion, and metastasis in endometrial cancer.

[464]

TÍTULO / TITLE: - Extracts from Epilobium sp. herbs induce apoptosis in human hormone-dependent prostate cancer cells by activating the mitochondrial pathway.

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

REVISTA / JOURNAL: - J Pharm Pharmacol. 2013 Jul;65(7):1044-54. doi: 10.1111/jphp.12063. Epub 2013 Apr 21.

●● Enlace al texto completo (gratis o de pago) 1111/jphp.12063

AUTORES / AUTHORS: - Stolarczyk M; Naruszewicz M; Kiss AK

INSTITUCIÓN / INSTITUTION: - Department of Pharmacognosy and Molecular Basis of Phytotherapy, Faculty of Pharmacy, Medical University of Warsaw, Warsaw, Poland.

RESUMEN / SUMMARY: - OBJECTIVES: The aim of this work was to determine the effect of standardized aqueous extracts from Epilobium angustifolium L., E. parviflorum Schreb. and E. hirsutum L. herbs on the apoptosis of hormone-dependent prostate cancer cells (LNCaP). METHODS: The extracts were

characterized using high-performance liquid chromatography-diode array detector coupled with mass spectrometry (HPLC-DAD-MS/MS). Apoptosis in the cells was analysed using Annexin V-fluorescein isothiocyanate, and mitochondrial potential, Deltapsim , using JC-1 by flow cytometry. Caspase-3 activity was determined by enzyme-linked immunosorbent assay. KEY FINDINGS: Using the HPLC-DAD-MS/MS method, 38 constituents were characterized. Extracts contained significant amounts of oenothien B as well as flavonoids and phenolic acids. Exposure of LNCaP cells to the extracts (20, 50 and 70 µg/ml) resulted in a significant increase in the level apoptotic cells, from 2.86 +/- 0.5% (for untreated cells) up to 86.6 +/- 1.0%. All extracts significantly decreased the mitochondrial potential, Deltapsim , resulting in an increase in the activity of caspase-3 from 0.3 +/- 0.07 ng/mg of protein (for untreated cells) up to 1.26 +/- 0.32 ng/mg of protein. CONCLUSIONS: This study demonstrated that Epilobium extracts are active against LNCaP prostate cancer cells and that their apoptotic activity is related to activation of the mitochondrial pathway. The high oenothien B content may influence the biological activity of these plant materials.

[465]

TÍTULO / TITLE: - Antiproliferative Effect of 1alpha,25-dihydroxyvitamin D3 Involves Upregulation of Cyclin-Dependent Kinase Inhibitor p21 in Human Pancreatic Cancer Cells.

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

REVISTA / JOURNAL: - Hepatogastroenterology. 2013 Jun;60(125):1199-205. doi: 10.5754/hge11073.

●● Enlace al texto completo (gratis o de pago) [5754/hge11073](#)

AUTORES / AUTHORS: - Kanemaru M; Maehara N; Chijiwa K

RESUMEN / SUMMARY: - Background/Aims: The aim of this study was to investigate the effect of 1alpha,25-dihydroxyvitamin D3 on proliferation of human pancreatic cancer cell lines and to identify related cell cycle regulatory proteins with antiproliferative effects. Methodology: Human pancreatic cancer cell lines SUI-2 and its four sublines, and Panc-1, AsPC-1, and MiaPaCa-2 were treated with 1alpha,25-dihydroxyvitamin D3. The number of cells was measured by the MTT method, and the cell cycle regulatory proteins were then analyzed by Western blotting. Results: Eight human pancreatic cancer cell lines expressed vitamin D receptor (VDR) mRNA. 1alpha,25-dihydroxyvitamin D3 inhibited proliferation of SUI-2 and its sublines. We found p21 to be upregulated after 24 hours in S2-028, the cell line in which proliferation was most inhibited by 1alpha,25-dihydroxyvitamin D3. Conclusions: 1alpha,25-dihydroxyvitamin D3 inhibited proliferation of pancreatic cancer cells and is involved in the upregulation of cyclin-dependent kinase inhibitor p21.

[466]

TÍTULO / TITLE: - Lycopene modulates growth and survival associated genes in prostate cancer.

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

REVISTA / JOURNAL: - J Nutr Biochem. 2013 Jun 5. pii: S0955-2863(13)00072-7. doi: 10.1016/j.jnutbio.2013.03.001.

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

[1016/j.jnutbio.2013.03.001](#)

AUTORES / AUTHORS: - Rafi MM; Kanakasabai S; Reyes MD; Bright JJ

INSTITUCIÓN / INSTITUTION: - Department of Food Science, School of Environmental and Biological Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ08901, USA.

RESUMEN / SUMMARY: - Lycopene is a fat soluble red-orange carotenoid pigment present in tomato that reduces the risk for prostate cancer, a common malignancy among men. However, the mechanism by which lycopene attenuates prostate cancer is not fully defined. In this study we examined the effect of lycopene on proliferation, survival, and biomarker gene expression in prostate cancer (PC-3) cells in culture. WST-1 assay showed that lycopene induces a biphasic effect on PC-3 cells with a modest increase in proliferation at 1-5 μ M, no change at 10-25 μ M and a decrease at 50-100 μ M doses in culture. Interestingly, combination treatment with lycopene induced anti-proliferative effect of Temozolomide on PC-3 cells. Lycopene also augmented the anti-proliferative effect of peroxisome proliferator-activated receptor gamma (PPAR γ) agonists, but not Doxorubicin or Taxol, in prostate cancer. Flow cytometry analyses showed that lycopene, in combination with chemotherapeutic agents and PPAR γ agonists, induced modest cell cycle arrest with significant increase in cell death by apoptosis and necrosis on prostate cancer. Gene array and quantitative reverse transcription polymerase chain reaction analyses showed that lycopene alters the expression of growth and apoptosis associated biomarkers in PC-3 cells. These findings highlight that lycopene attenuates prostate cancer by modulating the expression of growth and survival associated genes.

[467]

TÍTULO / TITLE: - Ethanol-induced apoptosis in human liver adenocarcinoma cells (SK-Hep1): Fas- and mitochondria-mediated pathways and interaction with MAPK signaling system.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 May 29;27(6):1820-1829. doi: 10.1016/j.tiv.2013.05.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.05.009](#)

AUTORES / AUTHORS: - Morio Y; Tsuji M; Inagaki M; Nakagawa M; Asaka Y; Oyamada H; Furuya K; Oguchi K

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, School of Medicine, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142-8555, Japan.

RESUMEN / SUMMARY: - For studying molecular mechanisms regulating the fate of ethanol-treated hepatocytes, involvement of Fas in ethanol-induced apoptosis was examined in human liver adenocarcinoma (SK-Hep1) cells in which the function of Fas-associated death domain (FADD) protein was knocked down by transfection. In FADD-knocked down cells, while ethanol-induced increase in generation of reactive oxygen species (ROS) was unaffected, apoptosis was significantly suppressed, demonstrating the involvement of Fas in ethanol-induced hepatocyte apoptosis more directly than in the past reports. On the other hand, effects of mitogen-activated protein kinase (MAPK), which is well known to determine the fate of various cells, on ethanol-induced apoptosis have not been examined in SK-Hep1 cells. Of three major MAPKs, only p38 MAPK and JNK were found activated by 200mM ethanol treatment. When cells were incubated with inhibitors of p38 MAPK and JNK, ethanol-induced apoptosis was decreased while ROS generation was unaffected, and examination of pro-apoptotic Bax and anti-apoptotic Bcl-2 levels showed decrease of the former and increase of the latter. We concluded that oxidative stress inflicted by ROS triggered Fas-mediated and mitochondria-mediated apoptotic pathways in ethanol-treated SK-Hep1 cells, and that p38 MAPK and JNK were promoting mitochondrial pathway, suggesting interaction between apoptosis and MAPK signaling systems.

[468]

TÍTULO / TITLE: - Estrogen receptor beta 2 is associated with poor prognosis in estrogen receptor alpha-negative breast carcinoma.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jul 2.

●● Enlace al texto completo (gratis o de pago) [1007/s00432-013-1467-](#)

[4](#)

AUTORES / AUTHORS: - Chantzi NI; Tiniakos DG; Palaiologou M; Goutas N; Filippidis T; Vassilaros SD; Dhimolea E; Mitsiou DJ; Alexis MN

INSTITUCIÓN / INSTITUTION: - Laboratory of Histology and Embryology, Medical School, University of Athens, 75 M. Asias str., 11527, Athens, Greece.

RESUMEN / SUMMARY: - **PURPOSE:** Our aim was to examine the prognostic significance of ERbeta1 and ERbeta2 expression in ERalpha-negative breast carcinomas. **MATERIALS AND METHODS:** We evaluated nuclear and cytoplasmic expression of ERbeta1 and ERbeta2 by immunohistochemistry in a group of 95 patients with long follow-up. ERbeta1 and ERbeta2 status was correlated with clinicopathological parameters and disease outcome. Univariate and multivariate analyses of ERbeta1 and ERbeta2 as independent markers of disease-free survival (DFS) were carried out using the Cox proportional hazards model. **RESULTS:** Nuclear ERbeta1 (nERbeta1) and nERbeta2 status was

positively correlated ($p = 0.01$). nERbeta1 positivity was associated with low histological grade ($p = 0.01$) in all patients and in the nERbeta2-positive subgroup ($p = 0.03$) but not in the nERbeta2-negative ($p = 0.27$). nERbeta2 positivity was associated with lymph node involvement and tumor relapse in all cases ($p < 0.00$ and $p < 0.00$, respectively) and in the nERbeta1-negative subgroup ($p < 0.00$ and $p < 0.00$, respectively) but not in the nERbeta1-positive ($p = 0.09$ and $p = 0.20$, respectively). nERbeta2 positivity was associated with poor DFS in all patients (log-rank $p < 0.00$), in the post-menopausal patient subgroup (log-rank $p = 0.02$) and in the HER2-negative (triple-negative) subgroup (log-rank $p = 0.04$). Cox multivariate analysis including ERbeta1, ERbeta2 and established clinicopathological variables highlighted ERbeta2 as an independent marker of early disease recurrence (hazard ratio 4.87; 95 % confidence interval 1.07-22.3; $p = 0.04$). CONCLUSION: High nERbeta2 is an independent marker of early relapse in ERalpha-negative breast carcinoma, and in particular, in the nERbeta1-negative, the post-menopausal patient and the triple-negative subgroups. These findings suggest that inhibition of expression and/or function of ERbeta2 could improve disease outcome.

[469]

TÍTULO / TITLE: - Polylysine-modified polyethylenimine inducing tumor apoptosis as an efficient gene carrier.

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

REVISTA / JOURNAL: - J Control Release. 2013 Jul 1. pii: S0168-3659(13)00373-8. doi: 10.1016/j.jconrel.2013.06.026.

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

[1016/j.jconrel.2013.06.026](#)

AUTORES / AUTHORS: - Tian H; Lin L; Jiao Z; Guo Z; Chen J; Gao S; Zhu X; Chen X

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China.

RESUMEN / SUMMARY: - Polyethylenimine (PEI) is receiving increasing attention as a gene carrier with high transfection efficiency. However, its high charge density and cytotoxic effects limit its application. Polylysine (PLL) is another polymeric gene carrier with good biodegradability and biocompatibility, although its lack of endosomal escape ability strongly impairs its transfection efficiency. In this study, PLL was introduced to PEI by ring-opening polymerization of epsilon-benzyloxycarbonyl-L-lysine N-carboxyanhydride, followed by deprotection of carbobenzyloxy groups. As-prepared PEI-PLL multiarm hyperbranched copolymers were characterized as gene carriers in vitro by measuring their particle size, zeta potential, cytotoxicity, transfection efficiency, and cell internalization. The optimum transfected efficiency of PEI-PLL was nearly seven times higher than that of PEI with a molecular weight of 25kDa.

Furthermore, pKH3-rev-casp-3 plasmid DNA was used as a gene for anti-tumor treatment in a xenograft model using nude mice. Compared with 25kDa PEI, PEI-PLL exhibited better tumor inhibition effects in 23days. In addition, terminal deoxynucleotidyl transferase dUTP nick end labeling, immunohistochemistry, and western blot analysis were used to determine the anti-tumor mechanism of PEI-PLL. The results showed that tumor cell apoptosis led to tumor inhibition, which could be attributed to pKH3-rev-casp-3 inducing poly(ADP-ribose) polymerase-1 cleavage. PEI-PLL is a promising gene carrier candidate for further application in vivo.

[470]

TÍTULO / TITLE: - Olaquinox-induced apoptosis is suppressed through p38 MAPK and ROS-mediated JNK pathways in HepG2 cells.

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

REVISTA / JOURNAL: - Cell Biol Toxicol. 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [1007/s10565-013-9249-](#)

[y](#)

AUTORES / AUTHORS: - Zhao WX; Tang SS; Jin X; Zhang CM; Zhang T; Wang CC; Sun Y; Xiao XL

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Toxicology, College of Veterinary Medicine, China Agricultural University, Beijing, 100193, People's Republic of China.

RESUMEN / SUMMARY: - We investigated mitogen-activated protein kinase (MAPK) pathways as well as reactive oxygen species (ROS) in olaquinox-induced apoptosis. Exposure of HepG2 cells to olaquinox resulted in the phosphorylation of p38 MAPK and c-Jun N-terminal kinases (JNK). To confirm the role of p38 MAPK and JNK, HepG2 cells were pretreated with MAPKs-specific inhibitors prior to olaquinox treatment. Olaquinox-induced apoptosis was significantly potentiated by the JNK inhibitor (SP600125) or the p38 MAPK inhibitor (SB203580). Furthermore, we observed that olaquinox treatment led to ROS generation and that olaquinox-induced apoptosis and ROS generation were both significantly reduced by the antioxidants, superoxide dismutase and catalase. In addition, the levels of phosphorylation of JNK, but not p38 MAPK, were significantly suppressed after pretreatment of the antioxidants, while inhibition of the activations of JNK or p38 MAPK had no effect on ROS generation. This result suggested that ROS may be the upstream mediator for the activation of JNK. Conclusively, our results suggested that apoptosis in response to olaquinox treatment in HepG2 cells might be suppressed through p38 MAPK and ROS-JNK pathways.

[471]

TÍTULO / TITLE: - Compound K Induces Apoptosis of Bladder Cancer T24 Cells Via Reactive Oxygen Species-Mediated p38 MAPK Pathway.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 Jul 30.

●● Enlace al texto completo (gratis o de pago) [1089/cbr.2012.1468](#)

AUTORES / AUTHORS: - Wang H; Jiang D; Liu J; Ye S; Xiao S; Wang W; Sun Z; Xie Y; Wang J

INSTITUCIÓN / INSTITUTION: - 1 Liaoning Key Laboratory of Food Biological Technology, School of Food Science and Technology, Dalian Polytechnic University, Dalian, China.

RESUMEN / SUMMARY: - Abstract Compound K (CK; 20-O-D-glucopyranosyl-20(S)-protopanaxadiol), a major metabolite of ginsenoside, has been shown to possess several biological activities such as potent antitumor properties. However, the effect of CK on the apoptosis of bladder cancer cells and its underlying mechanisms remain poorly understood. Therefore, we examined the effect of CK on the apoptosis of bladder cancer T 24 cells. Cell counts showed that treatment of T24 cells with CK decreased the cell number in a dose- and time-dependent manner. Flow cytometric analysis revealed that CK could significantly induce apoptosis of T24 cells in vitro. Further, cellular glutathione reduction, accumulation of reactive oxygen species (ROS) were also observed in CK-treated T24 cells. Western blot demonstrated the release of cytochrome c, activation of procaspases-3, procaspases-9, and the change of Bax/Bcl-2 proteins ratio. We also found that the phosphorylation of p38MAPK was increased by CK, while treatment with SB203580 inhibited CK-induced cell apoptosis in T24 cells. The blockage of ROS generation by N-acetylcysteine effectively prevented the apoptosis induction in T24 cells with CK treatment, accompanied by the decrease of activation of p38MAPK. These results suggested that CK induced the apoptosis of bladder cancer T24 cells, which is partially due to ROS generation and p38MAPK activation.

[472]

TÍTULO / TITLE: - Apoptotic toxicity of destruxin B in human non-Hodgkin lymphoma cells.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Jun 7;27(6):1870-1876. doi: 10.1016/j.tiv.2013.05.016.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.05.016](#)

AUTORES / AUTHORS: - Chao PZ; Chin YP; Hsu IU; Liu CM; Yu YC; Leung TK; Lee YJ; Chen CH; Lin YF

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; Department of Otolaryngology, Taipei Medical University Shuang-Ho Hospital, New Taipei, Taiwan.

RESUMEN / SUMMARY: - Destruxins are fungal toxins used as insecticides. Recent reports demonstrated the potential anti-cancer activities of destruxin B (DB). This study is to discover the effects of DB in lymphoma. Flow cytometry and Western blotting were used to analyze apoptosis and protein expression, respectively, in Toledo human non-Hodgkin lymphoma cells in response to DB. Administration of DB, induced apoptosis via death receptor pathway activating Fas associated death domain (FADD), caspase 8 and caspase 3, and suppressed the cell growth. In addition, DB altered mitochondrial membrane potential by increasing the expressions of tBid and Bax, but decreasing the levels of Bcl-2, resulting in the release of apoptosis-inducing factor (AIF). In conclusion, apoptosis of human non-Hodgkin lymphoma cells in response to DB is induced through the death receptor pathway and involves an alteration of the mitochondrial membrane potential. These findings may aid the development of novel treatment of non-Hodgkin lymphoma.

[473]

TÍTULO / TITLE: - MicroRNA-133^a, downregulated in osteosarcoma, suppresses proliferation and promotes apoptosis by targeting Bcl-xL and Mcl-1.

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

REVISTA / JOURNAL: - Bone. 2013 Sep;56(1):220-6. doi: 10.1016/j.bone.2013.05.020. Epub 2013 Jun 10.

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

[1016/j.bone.2013.05.020](#)

AUTORES / AUTHORS: - Ji F; Zhang H; Wang Y; Li M; Xu W; Kang Y; Wang Z; Wang Z; Cheng P; Tong D; Li C; Tang H

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Changhai Hospital, Second Military Medical University, Shanghai 200433, China.

RESUMEN / SUMMARY: - Deregulated microRNAs and their roles in cancer development have attracted much attention. Although miR-133^a has been shown to be important in osteogenesis, its roles in osteosarcoma carcinogenesis and progression remain unknown. Hence, we focused on the expression and mechanisms of miR-133^a in osteosarcoma development in this study. We found that miR-133^a was downregulated in osteosarcoma cell lines and primary human osteosarcoma tissues, and its decrease was significantly correlated with tumor progression and prognosis of the patients. Functional studies revealed that restoration of miR-133^a could reduce cell proliferation, promote cell apoptosis, and suppress tumorigenicity in osteosarcoma cell lines. Furthermore, bioinformatic prediction and experimental validation were applied to identify target genes of miR-133^a, and the results revealed that the anti-tumor effect of miR-133^a was probably due to targeting and repressing of Bcl-xL and Mcl-1 expression. Taken together, our data elucidate the roles of miR-133^a in osteosarcoma pathogenesis and implicate its potential in cancer therapy.

[474]

TÍTULO / TITLE: - Anti-proliferative effect of honokiol in oral squamous cancer through the regulation of specificity protein 1.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Jul 22. doi: 10.3892/ijo.2013.2028.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2028](#)

AUTORES / AUTHORS: - Kim DW; Ko SM; Jeon YJ; Noh YW; Choi NJ; Cho SD; Moon HS; Cho YS; Shin JC; Park SM; Seo KS; Choi JY; Chae JI; Shim JH

INSTITUCIÓN / INSTITUTION: - Department of Oral Pharmacology, School of Dentistry and Institute of Dental Bioscience, BK21 project, Chonbuk National University, Jeonju, Republic of Korea.

RESUMEN / SUMMARY: - Honokiol (HK), a novel plant-derived natural product, is a physiologically activated compound with polyphenolic structure, and has been identified to function as an anticancer agent. It has been widely used in several diseases as a traditional medicine for a long time. We investigated whether HK could show anticancer effects on two oral squamous cell lines (OSCCs), HN-22 and HSC-4. We demonstrated that HK-treated cells showed dramatic reduction in cell growth and apoptotic cell morphologies. Intriguingly, the transcription factor specificity protein 1 (Sp1) was significantly inhibited by HK in a dose-dependent manner. Furthermore, we checked changes in cell cycle regulatory proteins and anti-apoptotic proteins at the molecular level, which are known as Sp1 target genes. The important key regulators in the cell cycle such as p27 and p21 were up-regulated by HK-mediated down-regulation of Sp1, whereas anti-apoptotic proteins including Mcl-1 and survivin were decreased, resulting in caspase-dependent apoptosis. Taken together, results from this study suggest that HK could modulate Sp1 transactivation and induce apoptotic cell death through the regulation of cell cycle and suppression of antiapoptotic proteins. In addition, HK may be used in cancer prevention and therapies to improve the clinical outcome as an anticancer drug.

[475]

TÍTULO / TITLE: - Long non-coding RNA MEG3 inhibits the proliferation of cervical carcinoma cells through the induction of cell cycle arrest and apoptosis.

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

REVISTA / JOURNAL: - Neoplasma. 2013;60(5):486-92. doi: 10.4149/neo_2013_063.

●● Enlace al texto completo (gratis o de pago) [4149/neo_2013_063](#)

AUTORES / AUTHORS: - Qin R; Chen Z; Ding Y; Hao J; Hu J; Guo F

RESUMEN / SUMMARY: - Cervical cancer remains an important public health problem worldwide. New and effective therapeutic strategies targeting cervical cancer are urgently needed. Long non-coding RNAs (lncRNAs) are newly identified regulators in tumorigenesis and tumor progression. To investigate the

role of lncRNA MEG3 in the development of cervical cancer, we examined MEG3 expression in 18 pairs of cervical cancer and matched adjacent non-neoplastic tissues. Real-time quantitative RT-PCR (qRT-PCR) results showed high expression levels of MEG3 in non-neoplastic tissues, but markedly lower levels in cancer tissues. We further investigated whether the restoration of MEG3 expression might affect the proliferation of cervical carcinoma cells. Ectopic expression of MEG3 inhibited the proliferation of human cervical carcinoma cells HeLa and C-33^a in vitro. On the other hand, knockdown of MEG3 promoted the growth of well-differentiated cervical carcinoma HCC94 cells. Further investigation into the mechanisms responsible for the growth inhibitory effects revealed that overexpression of MEG3 resulted in the induction of G2/M cell cycle arrest and apoptosis. These results identified an important role of MEG3 in the molecular etiology of cervical cancer and implicated the potential application of MEG3 in cervical cancer therapy. Keywords: cervical cancer, long non-coding RNAs; MEG3, apoptosis.

[476]

TÍTULO / TITLE: - DNA methyltransferase inhibitors and their emerging role in epigenetic therapy of cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):2989-96.

AUTORES / AUTHORS: - Gnyszka A; Jastrzebski Z; Flis S

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, National Medicines Institute, Chelmska Street 30/34, 00-725 Warsaw, Poland.

sylwia.flis@yahoo.pl.

RESUMEN / SUMMARY: - The DNA methyltransferase (DNMT) inhibitors azacytidine and decitabine are the most successful epigenetic drugs to date and are still the most widely used as epigenetic modulators, even though their application for oncological diseases is restricted by their relative toxicity and poor chemical stability. Zebularine (1-(beta-D-ribofuranosyl)-1,2-dihydropyrimidin-2-one), a more stable and less toxic cytidine analog, is another inhibitor of DNMT with concomitant inhibitory activity towards cytidine deaminase. Unfortunately, there is no new information related to the possible clinical applications of zebularine. Although many new inhibitors of DNMT have been identified, none of them can so far replace azacytidine, decitabine and, to a lesser degree, zebularine. This review summarizes the current data and knowledge about azacytidine, decitabine and zebularine, and their role in present and possible future epigenetic cancer therapy. We also discuss the molecular modes of action of these agents with consideration of their different toxicities and demethylation profiles, reflecting their complex and partially overlapping biological effects.

PTPTPTP - Journal Article

[477]

TÍTULO / TITLE: - Cediranib in combination with fulvestrant in hormone-sensitive metastatic breast cancer: a randomized Phase II study.

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

REVISTA / JOURNAL: - Invest New Drugs. 2013 Jun 26.

- Enlace al texto completo (gratis o de pago) [1007/s10637-013-9991-](http://1007/s10637-013-9991-2)

[2](#)

AUTORES / AUTHORS: - Hyams DM; Chan A; de Oliveira C; Snyder R; Vinholes J; Audeh MW; Alencar VM; Lombard J; Mookerjee B; Xu J; Brown K; Klein P

INSTITUCIÓN / INSTITUTION: - Desert Regional Medical Center Comprehensive Cancer Center, Palm Springs, CA, USA.

RESUMEN / SUMMARY: - Hormone receptor-positive breast cancer is treated with estrogen inhibitors. Fulvestrant (FASLODEX), an estrogen receptor (ER) antagonist with no known agonist effects, competitively binds, blocks and degrades the ER. Vascular endothelial growth factor (VEGF) may mediate resistance to ER antagonists. Cediranib is a highly potent VEGF signaling inhibitor with activity against all three VEGF receptors. This randomized Phase II study evaluated cediranib plus fulvestrant. Postmenopausal women with hormone-sensitive metastatic breast cancer were eligible. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), duration of response, clinical benefit rate (CBR), safety/tolerability and pharmacokinetics (PK). Patients received cediranib 45 mg/day (n = 31) or placebo (n = 31) both plus fulvestrant.

Demographic/baseline characteristics were well balanced. Patients treated with cediranib had a numerical advantage in PFS (hazard ratio = 0.867, P = 0.669; median 223 vs. 112 days, respectively) and ORR (22 vs. 8 %, respectively) vs. placebo, although not statistically significant. CBR was 42 % in both arms. The most common adverse events (AEs) in the cediranib arm were diarrhea (68 %), fatigue (61 %) and hypertension (55 %). The incidence of grade ≥ 3 AEs (68 % vs. 32 %), serious AEs (48 % vs. 13 %), discontinuation AEs (39 % vs. 10 %), and cediranib dose reductions/interruptions (74 % vs. 32 %) were higher in the cediranib arm. There was no evidence of a clinically relevant effect of cediranib on fulvestrant PK. Cediranib plus fulvestrant may demonstrate clinical activity in this population, but cediranib 45 mg was not sufficiently well tolerated. Investigation of lower doses of cediranib plus hormonal/chemotherapy could be considered.

[478]

TÍTULO / TITLE: - Interleukin-17-producing cell infiltration in the breast cancer tumour microenvironment is a poor prognostic factor.

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

REVISTA / JOURNAL: - Histopathology. 2013 Aug;63(2):225-33. doi: 10.1111/his.12156. Epub 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) 1111/his.12156

AUTORES / AUTHORS: - Chen WC; Lai YH; Chen HY; Guo HR; Su IJ; Chen HH

INSTITUCIÓN / INSTITUTION: - Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

RESUMEN / SUMMARY: - AIMS: Interleukin-17 (IL-17) is a proinflammatory cytokine that is most prominently produced by T-helper type 17 (Th17) cells, a distinct CD4+ T-helper cell subset. The aim of this study was to investigate the level of IL-17-producing cells in the breast cancer tumour microenvironment and its prognostic role. METHODS AND RESULTS: A total of 207 breast carcinoma specimens were assessed by IL-17 immunohistochemistry, and the findings were correlated with clinicopathological parameters. We found that increased numbers of IL-17-producing cells were correlated with high histological grade, negative ER/PR status, and triple-negative molecular subtypes segregated by immunoprofiles. However, they did not correlate with stage, tumour size, nodal status, HER2 status, or histological type. Patients with tumours with high numbers of IL-17-producing cells had shorter disease-free survival (DFS) than patients with tumours with low numbers of IL-17-producing cells ($P < 0.01$). In multivariate analysis, high IL-17 level [hazard ratio (HR) 2.24; 95% CI 1.06-4.75], advanced T stage (HR 2.73; 95% CI 1.30-5.73), positive HER2 status (HR 4.88; 95% CI 1.47-16.18) and triple-negative subtype (HR 7.46; 95% CI 1.38-40.36) were significant prognostic factors for DFS. CONCLUSIONS: Our results indicate that a high level of IL-17-producing cells in the breast cancer tumour microenvironment is a poor prognostic factor.

[479]

TÍTULO / TITLE: - A Dendritic Cell Vaccine Pulsed with Autologous Hypochlorous Acid-Oxidized Ovarian Cancer Lysate Primes Effective Broad Antitumor Immunity: From Bench to Bedside.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Jul 15.

●● Enlace al texto completo (gratis o de pago) 1158/1078-0432.CCR-13-1185

AUTORES / AUTHORS: - Chiang CL; Kandalaf L; Tanyi JL; Hagemann AR; Motz GT; Svoronos N; Montone KT; Mantia-Smaldone GM; Smith L; Nisenbaum HL; Levine BL; Kalos M; Czerniecki BJ; Torigian DA; Powell DJ Jr; Mick R; Coukos G

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, University of Pennsylvania.

RESUMEN / SUMMARY: - PURPOSE: Whole tumor lysates are promising antigen sources for dendritic cell (DC) therapy for they contain many relevant

immunogenic epitopes to help prevent tumor escape. Two common methods of tumor lysate preparations are freeze-thaw processing and UVB-irradiation to induce necrosis and apoptosis, respectively. Hypochlorous acid (HOCl)-oxidation is a new method for inducing primary necrosis and enhancing the immunogenicity of tumor cells. EXPERIMENTAL DESIGN: We compared DCs' ability to engulf three different tumor lysate preparations, produce Th1-priming cytokines and chemokines, stimulate mixed leukocyte reactions (MLR), and finally elicit T-cell responses capable of controlling tumor growth in vivo. RESULTS: We demonstrated that DCs engulfed HOCl-oxidized lysate most efficiently, stimulated robust MLRs and elicited strong tumor-specific IFN-gamma secretions in autologous T-cells. These DCs produced the highest levels of Th1-priming cytokines and chemokines, including IL-12. Mice vaccinated with HOCl-oxidized ID8-ova lysate pulsed DCs developed T-cell responses that effectively controlled tumor growth. Safety, immunogenicity of autologous DCs pulsed with HOCl-oxidized autologous tumor lysate (OCDV vaccine), clinical efficacy and progression free survival (PFS) were evaluated in a pilot study of five subjects with recurrent ovarian cancer. OCDV vaccination produced few grade 1 toxicities and elicited potent T-cell responses against known ovarian tumor antigens. Circulating T regulatory cells and serum IL-10 were also reduced. Two subjects experienced durable PFS of >24 months after OCDV. CONCLUSIONS: This is the first study demonstrating the potential efficacy of a DC vaccine pulsed with HOCl-oxidized tumor lysate, a novel approach in preparing DC vaccine that is potentially applicable to many cancers.

[480]

TÍTULO / TITLE: - Serum Insulin-like Growth Factor-I Level Is an Independent Predictor of Recurrence and Survival in Early Hepatocellular Carcinoma: A Prospective Cohort Study.

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

REVISTA / JOURNAL: - Clin Cancer Res. 2013 Aug 1;19(15):4218-27. doi: 10.1158/1078-0432.CCR-12-3443. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [1158/1078-0432.CCR-12-3443](#)

AUTORES / AUTHORS: - Cho EJ; Lee JH; Yoo JJ; Choi WM; Lee MJ; Cho Y; Lee DH; Lee YB; Kwon JH; Yu SJ; Lee JM; Suh KS; Kim K; Kim YJ; Yoon JH; Kim CY; Lee HS

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: Department of Internal Medicine, Liver Research Institute, Departments of Radiology and Surgery, Seoul National University College of Medicine; and Samsung Fire & Marine Insurance Company, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - PURPOSE: Insulin-like growth factor-I (IGF-I) reflects hepatic synthetic function and plays an important role in the development and progression of various cancers. In this study, we investigated whether pretreatment serum IGF-I levels predict time-to-recurrence (TTR) and overall survival (OS) in patients with early-stage hepatocellular carcinoma after curative treatment. EXPERIMENTAL DESIGN: Consecutive patients with hepatocellular carcinoma who had undergone surgical resection, radiofrequency ablation, or percutaneous ethanol injection as curative treatments of early hepatocellular carcinoma were included from two prospective cohorts and the training set (n = 101) and the validation set (n = 91) were established. Serum samples were collected before treatment and the levels of IGF-I and IGF-binding protein-3 (IGFBP-3) were analyzed with regard to their associations with recurrence and survival. RESULTS: In the training set, patients with low IGF-I levels showed significantly shorter TTR [median, 14.6 months; 95% confidence interval (CI), 1.8-27.5] than patients with high IGF-I levels (median, 50.8 months; 95% CI, 36.9-64.7; P < 0.001) during a median follow-up period of 52.4 months. In the multivariate analysis, low levels of IGF-I were an independent predictor of recurrence (HR, 2.49; 95% CI, 1.52-4.08; P < 0.001). Furthermore, together with high-serum alpha-fetoprotein and multiple tumors, low levels of IGF-I remained an independent predictor of poorer survival (HR, 8.00; 95% CI, 1.94-33.01; P = 0.004). Applied to the independent validation set, low-serum IGF-I levels maintained their prognostic value for shorter TTR and OS. CONCLUSIONS: Low-baseline IGF-I levels independently correlated with shorter TTR and poorer survival in patients with early-stage hepatocellular carcinoma after curative treatment. Clin Cancer Res; 19(15); 4218-27. ©2013 AACR.

[481]

TÍTULO / TITLE: - Re: Prognostic Value of Blood mRNA Expression Signatures in Castration-resistant Prostate Cancer: A Prospective, Two-stage Study.

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

REVISTA / JOURNAL: - Eur Urol. 2013 Aug;64(2):341-2. doi: 10.1016/j.eururo.2013.05.014.

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

[1016/j.eururo.2013.05.014](#)

AUTORES / AUTHORS: - Maitland NJ

INSTITUCIÓN / INSTITUTION: - YCR Cancer Research Unit, Department of Biology, University of York, York, UK. Electronic address:

n.j.maitland@york.ac.uk.

[482]

TÍTULO / TITLE: - Selenocystine potentiates cancer cell apoptosis induced by 5-fluorouracil by triggering reactive oxygen species-mediated DNA damage and inactivation of the ERK pathway.

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

REVISTA / JOURNAL: - Free Radic Biol Med. 2013 Jul 6;65C:305-316. doi: 10.1016/j.freeradbiomed.2013.07.002.

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

[1016/j.freeradbiomed.2013.07.002](#)

AUTORES / AUTHORS: - Fan C; Chen J; Wang Y; Wong YS; Zhang Y; Zheng W; Cao W; Chen T

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, Jinan University, Guangzhou 510632, China.

RESUMEN / SUMMARY: - 5-Fluorouracil (5-FU)-based chemotherapy as a first-line treatment is quite limited, because of its inefficiency and clinical resistance to it. The search for chemosensitizers that could augment its efficiency and overcome the drug resistance to 5-FU has kindled great interest among scientists. Selenocystine (SeC), a naturally occurring selenoamino acid, displayed broad-spectrum anticancer activity in our previous studies. This study demonstrates that SeC acts as an effective enhancer of 5-FU-induced apoptosis in A375 human melanoma cells through induction of mitochondria-mediated apoptosis with the involvement of DNA damage-mediated p53 phosphorylation and ERK inactivation. Pretreatment of the cells with SeC significantly enhanced 5-FU-induced loss of mitochondrial membrane potential (psim) by regulating the expression levels of Bcl-2 family proteins. SeC and 5-FU in combination also triggered cell oxidative stress through regulation of the intracellular redox system and led to DNA damage and inactivation of ERK and AKT. Moreover, inhibitors of ERK and AKT effectively enhanced the apoptotic cell death induced by the combined treatment. However, pretreatment of the cells with glutathione reversed the apoptosis induced by SeC and 5-FU and recovered the expression of ERK and AKT inactivation, which revealed the important role of reactive oxygen species in cell apoptosis and regulation of ERK and AKT pathways. Taken together, our results suggest that a strategy of using SeC and 5-FU in combination could be a highly efficient way to achieve anticancer synergism.

[483]

TÍTULO / TITLE: - BAY 11-7082, a nuclear factor-kappaB inhibitor, induces apoptosis and S phase arrest in gastric cancer cells.

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

REVISTA / JOURNAL: - J Gastroenterol. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1007/s00535-013-0848-](#)

[4](#)

AUTORES / AUTHORS: - Chen L; Ruan Y; Wang X; Min L; Shen Z; Sun Y; Qin X

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai, 200032, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: Inhibitors of nuclear factor (NF)-kappaB pathway have shown potential anti-tumor activities. However, it is not fully elucidated in gastric cancer. METHODS: Firstly, we screened the inhibitory effect of pharmacologic NF-kappaB inhibitors on cell viability of human gastric cancer cells via CCK-8 assay. Next, cell apoptosis, cell cycle distribution, and mitochondrial membrane potential after BAY 11-7082 treatment were detected by annexin V staining, propidium iodide staining, TUNEL, and JC-1 assays in human gastric cancer HGC-27 cells. Expression of regulatory factors for apoptosis and cell cycle were measured by western blot. Finally, human gastric cancer xenograft model was established to verify the anti-tumor effects of BAY 11-7082 in vivo. Cellular apoptosis and growth inhibition in subcutaneous tumor section were detected by TUNEL and immunohistochemistry assays. RESULTS: BAY 11-7082 exhibited rapid and potent anti-tumor effects on gastric cancer cells in vitro within a panel of NF-kappaB inhibitors. BAY 11-7082 induced rapid apoptosis in HGC-27 cells through activating the mitochondrial pathway, as well as down-regulation of Bcl-2 and up-regulation of Bax. BAY 11-7082 also induced S phase arrest through suppressing Cyclin A and CDK-2 expression. Xenograft model confirmed the anti-tumor effects of BAY 11-7082 on apoptosis induction and growth inhibition in vivo. CONCLUSIONS: Our results demonstrated that BAY 11-7082 presented the most rapid and potent anti-tumor effects within a panel of NF-kappaB inhibitors, and could induce cellular apoptosis and block cell cycle progression both in vitro and in vivo, thus providing basis for clinical application of BAY 11-7082 in gastric cancer cases.

[484]

TÍTULO / TITLE: - Paeonol induces apoptosis in human ovarian cancer cells.

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

REVISTA / JOURNAL: - Acta Histochem. 2013 Jun 12. pii: S0065-1281(13)00076-7. doi: 10.1016/j.acthis.2013.04.004.

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

[1016/j.acthis.2013.04.004](#)

AUTORES / AUTHORS: - Yin J; Wu N; Zeng F; Cheng C; Kang K; Yang H

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, The Ninth People's Hospital of Chongqing, Chongqing 400700, PR China.

RESUMEN / SUMMARY: - Paeonol is a broad-spectrum antitumor agent, which is widely used in the treatment of various tumors in Asia. However, the effect of paeonol on ovarian cancer remains unclear. The purpose of this study was to investigate the effect of paeonol on ovarian cancer cells and its possible mechanism. Results measured by MTT (methyl thiazoyltetrazolium) assay showed that cell viability was markedly reduced in a dosage-dependent

manner, when treated with paeonol for 24h. Flow cytometry and Hoechst staining results indicated that the rate of apoptosis in the paeonol pretreatment group was higher than the control group. After co-culture with paeonol, cleaved Caspase 3 protein levels increased while survivin protein levels decreased. In conclusion, our findings indicate that paeonol can induce apoptosis of ovarian cancer cells via activation of Caspase 3 and down-regulation of survivin, and therefore is potentially an effective chemotherapeutic agent for ovarian cancer.

[485]

TÍTULO / TITLE: - Addition of rituximab to chemotherapy overcomes the negative prognostic impact of cyclin E expression in diffuse large B-cell lymphoma.

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

REVISTA / JOURNAL: - J Clin Pathol. 2013 Jun 17.

●● Enlace al texto completo (gratis o de pago) [1136/jclinpath-2013-201619](#)

AUTORES / AUTHORS: - Frei E; Visco C; Xu-Monette ZY; Dirnhofer S; Dybkaer K; Orazi A; Bhagat G; Hsi ED; van Krieken JH; Ponzoni M; Go RS; Piris MA; Moller MB; Young KH; Tzankov A

INSTITUCIÓN / INSTITUTION: - Institute of Pathology, University Hospital, Basel, Switzerland.

RESUMEN / SUMMARY: - BACKGROUND: High levels of cyclin E (CCNE) are accompanied by shorter survival in cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP)-treated diffuse large B-cell lymphomas (DLBCL), independent of the international prognostic index (IPI). Data on the prognostic role of CCNE in the 'rituximab era' are lacking. METHODS: To test reproducibility and applicability of observations from the 'pre-R era' to the 'R era', we examined the prognostic role of CCNE expression by immunohistochemistry in 1579 DLBCL on tissue microarrays (TMA); 339 patients were treated by CHOP and 635 by R-CHOP. RESULTS: 1209 samples (77%) were evaluable; failures were due to missing TMA punches and fixation artefacts. Mean expression of CCNE was 13% (0-85%); applying a cut-off of >16%, 382 DLBCL (31%) were positive. CCNE did not correlate with any of the known variables (IPI, primary site, cell of origin, proliferation, and BCL2- or C-MYC rearrangements). We were able to reproduce data suggesting an IPI- and response to therapy independent, negative prognostic impact of CCNE in CHOP-treated DLBCL patients: CCNE-positive cases had a median survival of 16 months compared with 57 months in negative ones (p=0.012). In R-CHOP-treated patients the prognostic impact of CCNE was abrogated and only IPI, cell of origin and response to therapy had a prognostic significance. CONCLUSIONS: Addition of R to CHOP overcomes the negative prognostic impact of CCNE in DLBCL. Thus, R not only prolongs survival in DLBCL but also serves a cautionary note that prognostic factors should not be transferred into the 'R era' without proper scientific studies.

[486]

TÍTULO / TITLE: - Different Apoptotic Effects of Triterpenoid Saponin-Rich Gypsophila oldhamiana Root Extract on Human Hepatoma SMMC-7721 and Normal Human Hepatic L02 Cells.

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

REVISTA / JOURNAL: - Biol Pharm Bull. 2013;36(7):1080-7.

AUTORES / AUTHORS: - Zhang W; Luo JG; Zhang C; Kong LY

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural Medicines, Department of Natural Medicinal Chemistry, China Pharmaceutical University.

RESUMEN / SUMMARY: - The roots of Gypsophila oldhamiana are rich in triterpenoid saponins with antitumor properties. Although previous reports have revealed the anticancer potency of some Gypsophila species, the underlying molecular mechanisms of this activity have not been studied in detail. The purpose of the present study was to prepare a triterpenoid saponin-rich G. oldhamiana root extract (TGOE) determined by LC-electrospray ionization (ESI)-MS(n) for biological studies and to evaluate the different anti-proliferative activities and apoptotic effects of TGOE on human hepatoma SMMC-7721 and normal human hepatic L02 cells. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay showed that TGOE selectively inhibited the proliferation of SMMC-7721 cells in a dose-dependent manner with IC50 value of 19.50±3.63 microg/mL, while the cytotoxic effects of TGOE on L02 cells were much lower with IC50 value of 40.48±3.74 microg/mL. Analysis of apoptotic morphological changes and flow cytometry indicated that TGOE might preferentially induce apoptosis in SMMC-7721 cells, while exhibited much lower effects on L02 cells. Western blot analysis showed that the different apoptotic effects of TGOE on SMMC-7721 and L02 cells were due to different protein regulation of caspase-3 and mitogen activated protein kinases (MAPKs). TGOE significantly activated caspase-3 and increased the phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), while decreased the phosphorylation of p38 in SMMC-7721 cells. However, the expression of these proteins was not statistically changed in L02 cells, except for the up-regulation of p38 phosphorylation. These results suggest that TGOE may have potential beneficial effects against hepatocellular carcinoma.

[487]

TÍTULO / TITLE: - Loss of the metastasis suppressor gene KiSS1 is associated with lymph node metastasis and poor prognosis in human colorectal cancer.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 20. doi: 10.3892/or.2013.2558.

●● [Enlace al texto completo \(gratis o de pago\) 3892/or.2013.2558](#)

AUTORES / AUTHORS: - Okugawa Y; Inoue Y; Tanaka K; Toiyama Y; Shimura T; Okigami M; Kawamoto A; Hiro J; Saigusa S; Mohri Y; Uchida K; Kusunoki M

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan.

RESUMEN / SUMMARY: - Cancer research is currently focused on blocking the metastatic process at its early steps. Some particularly attractive targets are metastasis suppressor genes, which control cancer cell dissemination. The aim of this study was to clarify the relationship between the expression of KiSS1, a metastasis suppressor gene, and disease progression in colorectal cancer patients. One-hundred and seventy-five patients who underwent surgery for colorectal cancer were enrolled in this study. We analyzed KiSS1 mRNA expression by real-time reverse transcription PCR in colorectal cancer tissue and paired adjacent normal mucosa. KiSS1 protein expression in early- and advanced-stage colorectal cancer samples was determined by immunohistochemical analysis. Decreased KiSS1 expression was significantly associated with lymph node metastasis and was an independent prognostic factor. Logistic regression analysis revealed that decreased KiSS1 expression was an independent risk factor for lymph node metastasis. Immunohistochemical analysis indicated that KiSS1 was highly expressed in the cell cytoplasm of early-stage colorectal cancer cells. The loss of KiSS1 appears to correlate with the progression of lymph node metastasis. An assessment of KiSS1 expression may assist in the accurate colorectal cancer diagnosis and may contribute to predict clinical outcomes.

[488]

TÍTULO / TITLE: - miR-381, a novel intrinsic WEE1 inhibitor, sensitizes renal cancer cells to 5-FU by up-regulation of Cdc2 activities in 786-O.

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

REVISTA / JOURNAL: - J Chemother. 2013;25(4):229-38. doi: 10.1179/1973947813Y.0000000092. Epub 2013 May 7.

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

[1179/1973947813Y.0000000092](#)

AUTORES / AUTHORS: - Chen B; Duan L; Yin G; Tan J; Jiang X

INSTITUCIÓN / INSTITUTION: - Department of Urology, Third Xiang-Ya Hospital of Central South University, Changsha, China.

RESUMEN / SUMMARY: - BACKGROUND: Few researches on increase of chemotherapy sensitivity by microRNA (miRNA) were reported. We aim to investigate exact role of miR-381 in chemotherapy sensitivity of 5-fluorouracil (5-FU) in renal cancer cells. METHODS: We investigated the cell survival, cell-cycle and apoptosis of 786-O and HK-2 cells treated with miR-381 and 5-FU. IC50 of 5-FU was calculated. To study apoptosis and G2/M arrest, we determined pHH3, mitotic index and caspase-3/7 activity. RESULTS: We

showed that miR-381 combined with 5-FU inhibited proliferation and potentiated the anti-tumour efficacies of 5-FU at tolerated concentration in vitro. miR-381 combined with 5-FU led to Cdc2 activation, mitotic catastrophe, and cell apoptosis through inhibitory WEE1. WEE1 was also validated as the direct target of miR-381. IC50 of 5-FU decreased significantly in the presence of miR-381. CONCLUSION: miR-381 increases sensitivity of 786-O cells to 5-FU by inhibitory WEE1 and increase of Cdc2 activity.

[489]

TÍTULO / TITLE: - Evaluation of p53 protein as a prognostic factor for oral cancer surgery.

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

REVISTA / JOURNAL: - Br J Oral Maxillofac Surg. 2013 Jun 19. pii: S0266-4356(13)00318-5. doi: 10.1016/j.bjoms.2013.05.150.

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

[1016/j.bjoms.2013.05.150](#)

AUTORES / AUTHORS: - Cutilli T; Leocata P; Dolo V; Altobelli E

INSTITUCIÓN / INSTITUTION: - Department of Life, Health & Environmental Sciences, Maxillofacial Surgery Unit, University of L'Aquila, Italy. Electronic address: tommaso.cutilli@cc.univaq.it.

RESUMEN / SUMMARY: - We have analysed concentrations of the p53 protein in advanced oral carcinomas immunohistochemically and genetically to detect the percentage of overexpression of this antioncogene that indicates a high probability of mutation. This would point to it being a useful prognostic factor, if we consider the importance of the relation between genetic alterations of p53 and poor overall survival. Seventy-five non-consecutive patients with oral squamous cell carcinoma and metastatic nodes were enrolled if there was homogeneity in histopathological grading (G2) of their tumours, and they were treated according to a multidisciplinary treatment plan. Monoclonal antibodies, extraction of DNA, and amplification of the polymerase chain reaction (PCR) were used for the immunohistochemical and genetic analyses. There was a significant inverse correlation between p53 overexpression and response to chemotherapy and a stronger association between high P53 overexpression (%) and a genetic mutation of p53 ($p=0.0001$). More than 50% overexpression indicated a strong probability of genetic mutation. There was no association between response to chemotherapy and age-groups or TNM classification ($p=0.2$), but there was a significant one between sex and site of tumour ($p<0.001$). Three prognostic factors were significantly related to prognosis: site of tumour ($p=0.01$), response to chemotherapy ($p=0.002$), and immuno p53 ($p=0.0001$). A tumour that is characterised by p53 overexpression of more than 50% indicates a poor prognosis.

[490]

TÍTULO / TITLE: - Antiproliferative effects of palladium(II) complexes of 5-nitrosopyrimidines and interactions with the proteolytic regulatory enzymes of the renin-angiotensin system in tumoral brain cells.

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

REVISTA / JOURNAL: - J Inorg Biochem. 2013 Sep;126:118-27. doi: 10.1016/j.jinorgbio.2013.06.005. Epub 2013 Jun 18.

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

1016/j.jinorgbio.2013.06.005

AUTORES / AUTHORS: - Illan-Cabeza NA; Garcia-Garcia AR; Martinez-Martos JM; Ramirez-Exposito MJ; Moreno-Carretero MN

INSTITUCIÓN / INSTITUTION: - Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, España.

RESUMEN / SUMMARY: - Seventeen new palladium(II) complexes of general formulae PdCl₂L, PdCl(LH-1)(solvent) and PdCl₂(PPh₃)₂L containing pyrimidine ligands derived from 6-amino-5-nitrosouracil and violuric acid have been prepared and characterized by elemental analysis, IR and NMR (¹H and ¹³C) methods and, two of them, PdCl(DANUH-1)(CH₃CN)·(1/2)H₂O and [PdCl(2MeOANUH-1)(CH₃CN)] by X-ray single-crystal diffraction (DANU: 6-amino-1,3-dimethyl-5-nitrosouracil; 2MeOANU: 6-amino-2-methoxy-5-nitroso-3H-pyrimidin-4-one). The coordination environment around palladium is nearly square planar in the two compounds with different supramolecular arrangements. Crystallographic and spectral data are consistent with a bidentate coordination mode through N5 and O4 atoms when the ligands act in neutral form and N5 and N6 atoms in the monodeprotonated ones. The cytotoxicity of the complexes against human neuroblastoma (NB69) and human glioma (U373-MG) cell lines has been tested showing a considerable antiproliferative activity. Also, the study of the effects of palladium(II) complexes on the renin-angiotensin system (RAS) regulating proteolytic regulatory enzymes aminopeptidase A (APA), aminopeptidase N (APN) and insulin-regulated aminopeptidase (IRAP) shows a strong dependence on the compound tested and the tumoral cell type, also affecting different catalytic routes; the compounds affect in a different way the activities of enzymes of the RAS system, changing their functional roles as initiators of cell proliferation in tumors as autocrine/paracrine mediators.

[491]

TÍTULO / TITLE: - Effects of Exogenous Zinc on Cell Cycle, Apoptosis and Viability of MDAMB231, HepG2 and 293 T Cells.

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

REVISTA / JOURNAL: - Biol Trace Elem Res. 2013 Jul 10.

●● Enlace al texto completo (gratis o de pago) [1007/s12011-013-9737-](http://1007/s12011-013-9737-1)

[1](#)

AUTORES / AUTHORS: - Wang YH; Li KJ; Mao L; Hu X; Zhao WJ; Hu A; Lian HZ; Zheng WJ

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Analytical Chemistry for Life Science, School of Chemistry and Chemical Engineering and Center of Materials Analysis, Nanjing University, 22 Hankou Road, Nanjing, 210093, China.

RESUMEN / SUMMARY: - As a non-toxic metal to humans, zinc is essential for cell proliferation, differentiation, regulation of DNA synthesis, genomic stability and mitosis. Zinc homeostasis in cells, which is crucial for normal cellular functioning, is maintained by various protein families including ZnT (zinc transporter/SLC30A) and ZIP (Zrt-, Irt-like proteins/SLC39A) that decrease and increase cytosolic zinc availability, respectively. In this study, we investigated the influences of a specific concentration range of ZnSO₄ on cell cycle and apoptosis by flow cytometry, and cell viability by MTT method in MDAMB231, HepG2 and 293 T cell lines. Fluorescent sensors NBD-TPEA and the counterstain for nuclei Hoechst 33342 were used to stain the treated cells for observing the localisation and amount of Zn²⁺ via laser scanning confocal microscope. It was found that the influence manners of ZnSO₄ on cell cycle, apoptosis and cell viability in various cell lines were different and corresponding to the changes of Zn²⁺ content of the three cell lines, respectively. The significant increase on intracellular zinc content of MDAMB231 cells resulted in cell death, G1 and G2/M cell cycle arrest and increased apoptotic fraction. Additionally, the mRNA expression levels of ZnT and ZIP families in the three cell lines, when treated with high concentration of ZnSO₄, increased and decreased corresponding to their functions, respectively.

[492]

TÍTULO / TITLE: - The integrin inhibitor cilengitide enhances the anti-glioma efficacy of vasculostatin-expressing oncolytic virus.

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

REVISTA / JOURNAL: - Cancer Gene Ther. 2013 Jul 5. doi: 10.1038/cgt.2013.38.

●● Enlace al texto completo (gratis o de pago) [1038/cgt.2013.38](#)

AUTORES / AUTHORS: - Fujii K; Kurozumi K; Ichikawa T; Onishi M; Shimazu Y; Ishida J; Chiocca EA; Kaur B; Date I

INSTITUCIÓN / INSTITUTION: - Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

RESUMEN / SUMMARY: - Oncolytic viral (OV) therapy has been considered as a promising treatment modality for brain tumors. Vasculostatin, the fragment of brain-specific angiogenesis inhibitor-1, shows anti-angiogenic activity against malignant gliomas. Previously, a vasculostatin-expressing oncolytic herpes simplex virus-1, Rapid Antiangiogenesis Mediated By Oncolytic virus (RAMBO), was reported to have a potent antitumor effect. Here, we investigated the

therapeutic efficacy of RAMBO and cilengitide, an integrin inhibitor, combination therapy for malignant glioma. In vitro, tube formation was significantly decreased in RAMBO and cilengitide combination treatment compared with RAMBO or cilengitide monotherapy. Moreover, combination treatment induced a synergistic suppressive effect on endothelial cell migration compared with the control virus. RAMBO, combined with cilengitide, induced synergistic cytotoxicity on glioma cells. In the caspase-8 and -9 assays, the relative absorption of U87DeltaEGFR cell clusters treated with cilengitide and with RAMBO was significantly higher than that of those treated with control. In addition, the activity of caspase 3/7 was significantly increased with combination therapy. In vivo, there was a significant increase in the survival of mice treated with combination therapy compared with RAMBO or cilengitide monotherapy. These results indicate that cilengitide enhanced vasculostatin-expressing OV therapy for malignant glioma and provide a rationale for designing future clinical trials combining these two agents. Cancer Gene Therapy advance online publication, 5 July 2013; doi:10.1038/cgt.2013.38.

[493]

TÍTULO / TITLE: - Differences in gene expression profiles and carcinogenesis pathways involved in cisplatin resistance of four types of cancer.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Aug;30(2):596-614. doi: 10.3892/or.2013.2514. Epub 2013 Jun 3.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2514](#)

AUTORES / AUTHORS: - Yang Y; Li H; Hou S; Hu B; Liu J; Wang J

INSTITUCIÓN / INSTITUTION: - Beijing Key Laboratory of Respiratory and Pulmonary Circulation, Capital Medical University, Beijing 100069, P.R. China.

RESUMEN / SUMMARY: - Cisplatin-based chemotherapy is the standard therapy used for the treatment of several types of cancer. However, its efficacy is largely limited by the acquired drug resistance. To date, little is known about the RNA expression changes in cisplatin-resistant cancers. Identification of the RNAs related to cisplatin resistance may provide specific insight into cancer therapy. In the present study, expression profiling of 7 cancer cell lines was performed using oligonucleotide microarray analysis data obtained from the GEO database. Bioinformatic analyses such as the Gene Ontology (GO) and KEGG pathway were used to identify genes and pathways specifically associated with cisplatin resistance. A signal transduction network was established to identify the core genes in regulating cancer cell cisplatin resistance. A number of genes were differentially expressed in 7 groups of cancer cell lines. They mainly participated in 85 GO terms and 11 pathways in common. All differential gene interactions in the Signal-Net were analyzed. CTNNB1, PLCG2 and SRC were the most significantly altered. With the use of bioinformatics, large amounts of data in microarrays were retrieved and analyzed by means of thorough

experimental planning, scientific statistical analysis and collection of complete data on cancer cell cisplatin resistance. In the present study, a novel differential gene expression pattern was constructed and further study will provide new targets for the diagnosis and mechanisms of cancer cisplatin resistance.

[494]

TÍTULO / TITLE: - Protein expression status in mucosal and submucosal portions of early gastric cancers and their predictive value for lymph node metastasis.

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

REVISTA / JOURNAL: - APMIS. 2013 Jun 12. doi: 10.1111/apm.12119.

●● Enlace al texto completo (gratis o de pago) [1111/apm.12119](http://dx.doi.org/10.1111/apm.12119)

AUTORES / AUTHORS: - Lee KB; Park DJ; Choe G; Kim HH; Kim WH; Lee HS

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Seoul National University College of Medicine, Seoul, 110-799, Korea.

RESUMEN / SUMMARY: - We aimed to find out predictive markers for lymph node (LN) metastasis of early gastric carcinoma (EGC) by separating evaluation of protein expression in mucosa and submucosa considering tumor heterogeneity. We selected 37 pN1-3 EGCs and depth- and size-matched 31 pN0 EGCs as training set and 72 EGCs including 14 pN1-3 EGCs as test set. Protein expression for beta-catenin, E-cadherin, N-cadherin, galectin-3, c-MET, TrkB, and Ki-67 was assessed by immunohistochemistry in mucosal (-m) and submucosal (-sm) portions of tumor. In the training set, Ki67-m was higher than in Ki67-sm (mean +/- SD: 82.67 +/- 11.99% vs 61.79 +/- 22.53%, $p < 0.001$). Altered E-cadherin-sm, high Ki67-m, and high Ki67-sm were correlated with LN metastasis ($p < 0.05$) and Ki67-sm was independent with lymphatic invasion and desmoplasia ($p = 0.015$ by multivariate logistic analysis). The test set confirmed Ki67-sm and E-cadherin-sm as predictors of LN metastasis ($p < 0.05$). Submucosal EGCs with ≥ 2 predictive factors out of high Ki67-sm, altered E-cadherin-sm, large tumor size (≥ 3 cm), diffuse type histology, and present lymphatic invasion yielded 100% sensitivity and 90.9% specificity for prediction of LN metastasis in 21 submucosal EGCs of test set. The proliferative activity of tumor in submucosa is suggested to be an independent predictor for LN metastasis in EGC.

[495]

TÍTULO / TITLE: - Nicotinamide mononucleotide adenylyltransferase2 overexpression enhances colorectal cancer cell-kill by Tiazofurin.

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

REVISTA / JOURNAL: - Cancer Gene Ther. 2013 Jul;20(7):403-12. doi: 10.1038/cgt.2013.33. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) [1038/cgt.2013.33](http://dx.doi.org/10.1038/cgt.2013.33)

AUTORES / AUTHORS: - Kusumanchi P; Zhang Y; Jani MB; Jayaram NH; Khan RA; Tang Y; Antony AC; Jayaram HN

INSTITUCIÓN / INSTITUTION: - 1] Research Service, Richard L. Roudebush Veterans Affairs Medical Center, Indianapolis, IN, USA [2] Department of Medicine (Hematology-Oncology), Indiana University School of Medicine, Indianapolis, IN, USA.

RESUMEN / SUMMARY: - Colorectal cancer cells exhibit limited cytotoxicity towards Tiazofurin, a pro-drug metabolized by cytosolic nicotinamide mononucleotide adenylyltransferase2 (NMNAT2) to thiazole-4-carboxamide adenine dinucleotide, a potent inhibitor of inosine 5'-monophosphate dehydrogenase required for cellular guanylate synthesis. We tested the hypothesis that colorectal cancer cells that exhibit low levels of NMNAT2 and are refractory to Tiazofurin can be rendered sensitive to Tiazofurin by overexpressing NMNAT2. Transfection of hNMNAT2 resulted in a six- and threefold cytoplasmic overexpression in Caco2 and HT29 cell lines correlating with Tiazofurin-induced enhanced cell-kill. Folate receptors expressed on the cell surface of 30-50% colorectal carcinomas were exploited for cellular targeting with Tiazofurin encapsulated in folate-tethered nanoparticles. Our results indicated that in wild-type colorectal cancer cells, free Tiazofurin-induced EC50 cell-kill was 1500-2000 μM , which was reduced to 66-156 μM in hNMNAT2-overexpressed cells treated with Tiazofurin encapsulated in non-targeted nanoparticles. This efficacy was improved threefold by encapsulating Tiazofurin in folate-tethered nanoparticles to obtain an EC50 cell-kill of 22-59 μM , an equivalent of 100-300 mg m^{-2} (one-tenth of the approved dose of Tiazofurin in humans), which will result in minimal toxicity leading to cancer cell-kill. This proof-of-principle study suggests that resistance of colorectal cancer cell-kill to Tiazofurin can be overcome by sequentially overexpressing hNMNAT2 and then facilitating the uptake of Tiazofurin by folate-tethered nanoparticles, which enter cells via folate receptors.

[496]

TÍTULO / TITLE: - P-glycoprotein (MDR1/ABCB1) and breast cancer resistance protein (BCRP/ABCG2) restrict brain accumulation of the JAK1/2 inhibitor, CYT387.

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

REVISTA / JOURNAL: - Pharmacol Res. 2013 Jul 1;76C:9-16. doi: 10.1016/j.phrs.2013.06.009.

●● Enlace al texto completo (gratis o de pago) [1016/j.phrs.2013.06.009](https://doi.org/10.1016/j.phrs.2013.06.009)

AUTORES / AUTHORS: - Durmus S; Xu N; Sparidans RW; Wagenaar E; Beijnen JH; Schinkel AH

INSTITUCIÓN / INSTITUTION: - The Netherlands Cancer Institute, Division of Molecular Oncology, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.

RESUMEN / SUMMARY: - CYT387 is an orally bioavailable, small molecule inhibitor of Janus family of tyrosine kinases (JAK) 1 and 2. It is currently undergoing Phase I/II clinical trials for the treatment of myelofibrosis and myeloproliferative neoplasms. We aimed to establish whether the multidrug efflux transporters P-glycoprotein (P-gp; MDR1; ABCB1) and breast cancer resistance protein (BCRP;ABCG2) restrict oral availability and brain penetration of CYT387. In vitro, CYT387 was efficiently transported by both human MDR1 and BCRP, and very efficiently by mouse Bcrp1 and its transport could be inhibited by specific MDR1 inhibitor, zosuquidar and/or specific BCRP inhibitor, Ko143. CYT387 (10mg/kg) was orally administered to wild-type (WT), Bcrp1^{-/-}, Mdr1a/1b^{-/-} and Bcrp1;Mdr1a/1b^{-/-} mice and plasma and brain concentrations were analyzed. Over 8h, systemic exposure of CYT387 was similar between all the strains, indicating that these transporters do not substantially limit oral availability of CYT387. Despite the similar systemic exposure, brain accumulation of CYT387 was increased 10.5- and 56-fold in the Bcrp1;Mdr1a/1b^{-/-} mice compared to the WT strain at 2 and 8h after CYT387 administration, respectively. In single Bcrp1^{-/-} mice, brain accumulation of CYT387 was more substantially increased than in Mdr1a/1b^{-/-} mice, suggesting that CYT387 is a slightly better substrate of Bcrp1 than of Mdr1a at the blood-brain barrier. These results indicate a marked and additive role of Bcrp1 and Mdr1a/1b in restricting brain penetration of CYT387, potentially limiting efficacy of this compound against brain (micro) metastases positioned behind a functional blood-brain barrier.

[497]

TÍTULO / TITLE: - Predictive Model for Epoxide Hydrolase-Generated Stereochemistry in the Biosynthesis of Nine-Membered Eneidyne Antitumor Antibiotics.

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

REVISTA / JOURNAL: - Biochemistry. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1021/bi400572a](#)

AUTORES / AUTHORS: - Horsman GP; Lechner A; Ohnishi Y; Moore BS; Shen B

INSTITUCIÓN / INSTITUTION: - Division of Pharmaceutical Sciences, University of Wisconsin-Madison, Madison, Wisconsin 53705, United States.

RESUMEN / SUMMARY: - Nine-membered enediyne antitumor antibiotics C-1027, neocarzinostatin (NCS), and kedarcidin (KED) possess enediyne cores to which activity-modulating peripheral moieties are attached via R^{\ominus} - or (S)-vicinal diols. We have previously shown that this stereochemical difference arises from hydrolysis of epoxide precursors by epoxide hydrolases (EHs) with different regioselectivities. The inverting EHs, such as SgcF, hydrolyze an (S)-epoxide substrate to yield an R^{\ominus} -diol in C-1027 biosynthesis, whereas the retaining EHs, such as NcsF2 and KedF, hydrolyze an (S)-epoxide substrate to yield an (S)-diol in NCS and KED biosynthesis. We now report the characterization of a

series of EH mutants and provide a predictive model for EH regioselectivity in the biosynthesis of the nine-membered enediyne antitumor antibiotics. A W236Y mutation in SgcF increased the retaining activity toward (S)-styrene oxide by 3-fold, and a W236Y/Q237M double mutation in SgcF, mimicking NcsF2 and KedF, resulted in a 20-fold increase in the retaining activity. To test the predictive utility of these mutations, two putative enediyne biosynthesis-associated EHs were identified by genome mining and confirmed as inverting enzymes, SpoF from *Salinospora tropica* CNB-440 and SgrF (SGR_625) from *Streptomyces griseus* IFO 13350. Finally, phylogenetic analysis of EHs revealed a familial classification according to inverting versus retaining activity. Taken together, these results provide a predictive model for vicinal diol stereochemistry in enediyne biosynthesis and set the stage for further elucidating the origins of EH regioselectivity.

[498]

TÍTULO / TITLE: - Small-molecule multi-targeted kinase inhibitor RGB-286638 triggers P53-dependent and -independent anti-multiple myeloma activity through inhibition of transcriptional CDKs.

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

REVISTA / JOURNAL: - Leukemia. 2013 Jun 28. doi: 10.1038/leu.2013.194.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.194](#)

AUTORES / AUTHORS: - Cirstea D; Hideshima T; Santo L; Eda H; Mishima Y; Nemani N; Hu Y; Mimura N; Cottini F; Gorgun G; Ohguchi H; Suzuki R; Loferer H; Munshi NC; Anderson KC; Raje N

INSTITUCIÓN / INSTITUTION: - 1] MGH Cancer Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA [2] Leebow Institute of Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Disease Center, Dana-Farber Cancer Institute, Boston, MA, USA.

RESUMEN / SUMMARY: - Small-molecule multi-targeted cyclin-dependent kinase (CDK) inhibitors (CDKIs) are of particular interest due to their potent antitumor activity independent of p53 gene alterations. P53 deletion is associated with a very poor prognosis in multiple myeloma (MM). In this regard, we tested the anti-MM activity of RGB-286638, an indenopyrazole-derived CDKI with Ki-nanomolar activity against transcriptional CDKs. We examined RGB-286638's mode-of-action in MM cell lines with wild-type (wt)-p53 and those expressing mutant p53. RGB-286638 treatment resulted in MM cytotoxicity in vitro associated with inhibition of MM tumor growth and prolonged survival in vivo. RGB-286638 displayed caspase-dependent apoptosis in both wt-p53 and mutant-p53 cells that was closely associated with the downregulation of RNA polymerase II phosphorylation and inhibition of transcription. RGB-286638 triggered p53 accumulation via nucleolar stress and loss of Mdm2, accompanied by induction of p53 DNA-binding activity. In addition, RGB-286638 mediated p53-independent activity, which was confirmed by cytotoxicity

in p53-knockdown and p53-mutant cells. We also demonstrated downregulation of oncogenic miR-19, miR-92^a-1 and miR-21. Our data provide the rationale for the development of transcriptional CDKIs as therapeutic agents, which activate p53 in competent cells, while circumventing p53 deficiency through alternative p53-independent cell death mechanisms in p53-mutant/deleted cells. Leukemia advance online publication, 26 July 2013; doi:10.1038/leu.2013.194.

[499]

TÍTULO / TITLE: - Phenethyl isothiocyanate suppresses EGF-stimulated SAS human oral squamous carcinoma cell invasion by targeting EGF receptor signaling.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Aug;43(2):629-37. doi: 10.3892/ijo.2013.1977. Epub 2013 Jun 7.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.1977](#)

AUTORES / AUTHORS: - Chen HJ; Lin CM; Lee CY; Shih NC; Amagaya S; Lin YC; Yang JS

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Molecular Systems Biomedicine, China Medical University, Taichung 404, Taiwan, R.O.C.

RESUMEN / SUMMARY: - Phenethyl isothiocyanate (PEITC) is a natural compound that is involved in chemoprevention as well as inhibition of cell growth and induction of apoptosis in several types of cancer cells. Previous studies have revealed that PEITC suppresses the invasion of AGS gastric and HT-29 colorectal cancer cells. However, the effects of PEITC on the metastasis of SAS oral cancer cells remain to be determined. Our results showed that PEITC treatment inhibited the invasion of EGF-stimulated SAS cells in a concentration-dependent manner, but appeared not to affect the cell viability. The expression and enzymatic activities of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) were suppressed by PEITC. Concomitantly, we observed an increase in the protein expression of both tissue inhibitor of metalloproteinase-1 (TIMP-1) and -2 (TIMP-2) in treated cells. Furthermore, PEITC treatments decreased the protein phosphorylation of epidermal growth factor receptor (EGFR) and downstream signaling proteins including PDK1, PI3K (p85), AKT, phosphorylated IKK and IκappaB to inactivate NF-κappaB for the suppression of MMP-2 and MMP-9 expression. In addition, PEITC can trigger the MAPK signaling pathway through the increase in phosphorylated p38, JNK and ERK in treated cells. Our data indicate that PEITC is able to inhibit the invasion of EGF-stimulated SAS oral cancer cells by targeting EGFR and its downstream signaling molecules and finally lead to the reduced expression and enzymatic activities of both MMP-2 and MMP-9. These results suggest that PEITC is promising for the therapy of oral cancer metastasis.

[500]

TÍTULO / TITLE: - Prognostic and Putative Predictive Biomarkers of Gastric Cancer for Personalized Medicine.

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

REVISTA / JOURNAL: - Diagn Mol Pathol. 2013 Jul 9.

- Enlace al texto completo (gratis o de pago)

[1097/PDM.0b013e318284188e](#)

AUTORES / AUTHORS: - Warneke VS; Behrens HM; Haag J; Balschun K; Boger C; Becker T; Ebert MP; Lordick F; Rocken C

INSTITUCIÓN / INSTITUTION: - Departments of *Pathology double daggerGeneral Surgery and Thoracic Surgery, Christian-Albrechts-University, Kiel daggerDepartment of Pathology, Charite University Hospital, Berlin section signDepartment of Medicine II, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Mannheim parallelUniversity Cancer Center Leipzig (UCCL), University of Leipzig, Leipzig, Germany.

RESUMEN / SUMMARY: - We investigated various phenotypic and genotypic biomarkers of gastric cancer (GC) testing the following hypotheses: are these biomarkers suitable for the identification of GC subtypes, are they of prognostic significance, and should any of these biomarkers be considered to tailor patient treatment in the future. The study cohort consisted of 482 patients. pTNM-stage was based on surgical pathologic examination. The Lauren and mucin phenotype was assessed. Helicobacter pylori and Epstein-Barr virus infections were documented. The following biomarkers were determined: BRAF, KRAS, NRAS, and PIK3CA genotype, microsatellite instability, mucin 1, mucin 2, mucin 5, and mucin 6, CD10, E-cadherin, beta-catenin, and lysozyme. The histologic phenotype correlated with 10/13 (77%) clinicopathologic patient characteristics and 6/13 (46%) immunohistochemical/molecular biological biomarkers. Inversely, immunohistochemical biomarkers (mucin phenotype, E-cadherin, beta-catenin, and lysozyme) were unsuitable for subclassification of GC. It showed too much overlap between the different subtypes. Among the genotypes, only microsatellite instability correlated with tumor type being more prevalent in intestinal and unclassified GCs. Patient survival correlated significantly with 8 (62%) clinicopathologic and 5 (36%) immunohistochemical/molecular biomarkers. Interestingly, in proximal GCs, KRAS mutation was associated with worse prognosis, as was persistent H. pylori infection in unclassified GCs. Mucin 2 (all patients, proximal GCs) and PIK3CA (exon 20; intestinal type GC) prognosticated independently patient survival. The biomarkers examined herein are unsuitable to aid histologic classification of GC. However, several of them show a correlation with either phenotype and/or prognosis and may be considered to tailor patient treatment in the future, such as KRAS, PIK3CA, MSI, and H. pylori status.

[501]

TÍTULO / TITLE: - Riccardin D induces cell death by activation of apoptosis and autophagy in osteosarcoma cells.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 Jun 27;27(6):1928-1936. doi: 10.1016/j.tiv.2013.06.001.

●● Enlace al texto completo (gratis o de pago) [1016/j.tiv.2013.06.001](#)

AUTORES / AUTHORS: - Wang Y; Ji Y; Hu Z; Jiang H; Zhu F; Yuan H; Lou H

INSTITUCIÓN / INSTITUTION: - Department of Natural Product Chemistry, Key Lab of Chemical Biology of MOE (Ministry of Education), Shandong University, Jinan 250012, China.

RESUMEN / SUMMARY: - Macrocyclic bisbibenzyls, characteristic components derived from liverworts, have various biological activities. Riccardin D (RD), a liverwort-derived naturally occurring macrocyclic bisbibenzyl, has been found to exert anticancer effects in multiple cancer cell types through apoptosis induction. However, the underlying mechanisms of such effects remain undefined. In addition, whether RD induces other forms of cell death such as autophagy is unknown. In this study, we found that the arrest of RD-caused U2OS (p53 wild) and Saos-2 (p53 null) cells in G1 phase was associated with the induction of p53 and p21WAF1 in U2OS cells. RD-mediated cell cycle arrest was accompanied with apoptosis promotion as indicated by changes in nuclear morphology and expression of apoptosis-related proteins. Further studies revealed that the antiproliferation of RD was unaffected in the presence of p53 inhibitor but was partially reversed by a pan-inhibitor of caspases, suggesting that p53 was not required in RD-mediated apoptosis and that caspase-independent mechanisms were involved in RD-mediated cell death. Except for apoptosis, RD-induced autophagy occurred as evidenced by the accumulation of microtubule-associated protein-1 light chain-3B-II, formation of AVOs, punctate dots, and increased autophagic flux. Pharmacological blockade of autophagy activation markedly attenuated RD-mediated cell death. RD-induced cell death was significantly restored by the combination of autophagy and caspase inhibitors in osteosarcoma cells. Overall, our study revealed RD-induced caspase-dependent apoptosis and autophagy in cancer cells, as well as highlighted the importance of continued investigation on the use of RD as a potential anticancer candidate.

[502]

TÍTULO / TITLE: - Keratinocytes and head and neck squamous cell carcinoma cells regulate urokinase-type plasminogen activator and plasminogen activator inhibitor-1 in fibroblasts.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3113-8.

AUTORES / AUTHORS: - Hakelius M; Koskela A; Ivarsson M; Grenman R; Rubin K; Gerdin B; Nowinski D

INSTITUCIÓN / INSTITUTION: - Department of Surgical Sciences, Plastic Surgery, Uppsala University, 751 85 Uppsala, Sweden. malin.hakelius@akademiska.se.

RESUMEN / SUMMARY: - BACKGROUND: To investigate possible differences in the effects of soluble factors from oral squamous cell carcinoma (SCC) cells (UT-SCC-87) and normal oral keratinocytes (NOK) on fibroblast expression of genes involved in tumor stroma turnover. MATERIALS AND METHODS: Transwell co-cultures with fibroblasts in collagen gels, and SCC cells or NOK in inserts were carried out. Fibroblast gene expression was measured with real-time polymerase chain reaction (PCR). RESULTS: The expression of urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) was up-regulated in co-cultures with SCC cells but not with NOK. In contrast, both SCC cells and NOK regulated matrix metalloproteinase-1 (MMP1) and -3, and tissue inhibitor of metalloproteinases-2 (TIMP2) and -3 to a similar extent, while MMP2 and TIMP1 were largely unaffected. Interleukin 1 alpha (IL1alpha) up-regulated both MMP1 and MMP3 and down-regulated PAI-1, TIMP2 and -3. CONCLUSION: SCC and NOK regulate fibroblast expression of genes involved in tumor stroma turnover differentially in vitro. These observations may contribute to a better understanding of the mechanisms behind extracellular matrix turnover in tumors.

[503]

TÍTULO / TITLE: - CHFR silencing or microsatellite instability is associated with increased anti-tumor activity of docetaxel or gemcitabine in colorectal cancer.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jul 20. doi: 10.1002/ijc.28390.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28390](https://doi.org/10.1002/ijc.28390)

AUTORES / AUTHORS: - Pelosof L; Yerram SR; Ahuja N; Delmas A; Danilova L; Herman JG; Azad NS

INSTITUCIÓN / INSTITUTION: - Cancer Biology Program, Johns Hopkins University School of Medicine, Baltimore, Maryland.

RESUMEN / SUMMARY: - Phenotypic differences among cancers with the same origin may be associated with chemotherapy response. CHFR silencing associated with DNA methylation has been suggested to be predictive of taxane sensitivity in diverse tumor types. However, the use of microsatellite instability (MSI:unstable—MSS:stable) as a predictive marker for therapeutic effect has had conflicting results. We examined these molecular alterations as predictors of chemotherapy sensitivity in colorectal cancer (CRC). Differential sensitivity to docetaxel and gemcitabine was compared to potential predictive biomarkers CHFR methylation and MSI status. Cell lines that were MSI-H/CHFR-methylated, MSS/CHFR-methylated, and MSS/CHFR-unmethylated were assessed for in vivo sensitivity of CRC cell line xenografts to docetaxel and/or

gemcitabine. We observed increased sensitivity in vitro to gemcitabine in cell lines with MSI and docetaxel in cell lines with CHFR inactivation via DNA methylation. In vivo treatment of human xenografts confirmed differential sensitivity, with the MSI-H/CHFR-methylated line RKO having tumor growth inhibition to each agent, and at least additive tumor growth inhibition with combination therapy. The MSS-CHFR-unmethylated line, CACO2, was resistant to single and combination therapy, while COLO205, the MSS/CHFR-methylated line, showed tumor growth inhibition with docetaxel, but not gemcitabine, therapy. CHFR methylation in CRC cell lines predicted for sensitivity in vitro and in vivo to docetaxel, while MSI-H cell lines were more sensitive to gemcitabine. These data suggest that a subset of CRC patients would be selectively sensitive to a novel combination of gemcitabine and docetaxel, and are the basis for an ongoing clinical trial of this combination in a biomarker-selected patient population. © 2013 Wiley Periodicals, Inc.

[504]

TÍTULO / TITLE: - Comparison of the Time-to-response Between Radiotherapy and Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitors for Advanced Non-small Cell Lung Cancer with EGFR Mutation.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3279-84.

AUTORES / AUTHORS: - Imai H; Shukuya T; Takahashi T; Fujiwara S; Mori K; Ono A; Akamatsu H; Taira T; Kenmotsu H; Naito T; Kaira K; Murakami H; Harada H; Endo M; Nakajima T; Yamamoto N

INSTITUCIÓN / INSTITUTION: - Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-chou, Suntou-gun, Shizuoka 411-8777, Japan. Tel: +81 559895222, m06701014@gunma-u.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: Patients harboring sensitive epidermal growth factor receptor (EGFR) mutations show a dramatic response to treatment with EGFR tyrosine kinase inhibitors (TKIs). However, there have been no clinical reports in lung cancer patients that compare the time-to-response between radiotherapy and EGFR-TKIs. PATIENTS AND METHODS: We reviewed 17 and 32 consecutive patients with inoperable stage III/IV NSCLC who harbored sensitive EGFR mutations and who were treated with thoracic radiotherapy with or without chemotherapy and EGFR-TKIs, respectively. RESULTS: There were statistically significant differences in time-to-partial response (PR) with regard to the treatment modalities (radiotherapy vs. EGFR-TKIs, median 57 days vs. 22 days, log-rank test, p=0.008). CONCLUSION: EGFR-TKIs elicit tumor shrinkage earlier than does radiotherapy in patients with a sensitive EGFR mutation, suggesting that EGFR-TKIs may be useful for early symptom improvement in these patients.

[505]

TÍTULO / TITLE: - Apoptosis induced by paclitaxel via Bcl-2, Bax and caspases 3 and 9 activation in NB4 human leukaemia cells is not modulated by ERK inhibition.

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

REVISTA / JOURNAL: - Exp Toxicol Pathol. 2013 Jun 1. pii: S0940-2993(13)00058-4. doi: 10.1016/j.etp.2013.04.006.

●● Enlace al texto completo (gratis o de pago) 1016/j.etp.2013.04.006

AUTORES / AUTHORS: - Morales-Cano D; Calvino E; Rubio V; Herraiz A; Sancho P; Tejedor MC; Diez JC

INSTITUCIÓN / INSTITUTION: - Bioquímica y Biología Molecular, Facultad de Medicina, Campus Universitario, Universidad de Alcalá, 28871 Alcalá de Henares (Madrid), España.

RESUMEN / SUMMARY: - We have studied the role of pivotal bio-molecules involved in signalling of cytotoxic effects induced by paclitaxel (Ptx) on acute promyelocytic human leukaemia NB4 cells. A time-dependent increase in cell death and DNA cleavage was observed after 30µM Ptx treatment. Cell death induction by Ptx proceeds mainly as programmed cell death as shown by annexin V-FITC, reaching up to 30% of apoptotic cells after 24h. Significant reductions of p53, changes in Bax and Bcl-2 and activation of caspases 3 and 9 were observed as the treatment was applied for long times. Ptx treatments produced NFκB depletion with expression levels abolished at 19h what could be involved in reduction of survival signals. Phosphorylation of intracellular kinases showed that pERK1/2 decreased significantly at 19h of Ptx treatment. When these cells were preincubated for 90min with 20µM PD98059, 2'-amino-3'-methoxyflavone, an inhibitor of ERK phosphorylation, a slight reduction of cell viability was observed in comparison to that produced by Ptx alone. Pretreatment with PD98059 neither activated caspases nor significantly increased the apoptotic effect of Ptx. Taken together, our data reveal that the inhibition of ERK phosphorylation does not seem to be an essential pathway for bursting an increased induction of apoptosis by Ptx. Decrease of p53 and Bcl-2, fragmentation of DNA, increase of Bax and, finally, activation of caspases 3 and 9 in NB4 leukaemia cells make the apoptotic process induced by Ptx irreversible. Application of Ptx in leukaemia cells shows therefore a promising potential with particular effects on different leukaemia cell types.

[506]

TÍTULO / TITLE: - Tumor suppressor in lung cancer 1 (TSLC1), a novel tumor suppressor gene, is implicated in the regulation of proliferation, invasion, cell cycle, apoptosis, and tumorigenicity in cutaneous squamous cell carcinoma.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0961-](#)

[2](#)

AUTORES / AUTHORS: - Liu D; Feng X; Wu X; Li Z; Wang W; Tao Y; Xia Y

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, the First Affiliated Hospital of Xinxiang Medical University, No. 88, Health Road, Weihui, Henan, 453100, China.

RESUMEN / SUMMARY: - Tumor suppressor in lung cancer 1 (TSLC1) is tightly implicated in a variety of biological processes and plays critical roles in tumor development and progression. However, the roles of TSLC1 in cutaneous squamous cell carcinoma (CSCC) remain to be unraveled. Here, we reported the TSLC1 gene that was significantly downregulated in CSCC tissues and cells, and survival times of patients with TSLC1 at a low level were markedly lower than that at a high level ($P = 0.0070$). A stepwise investigation demonstrated that an elevated TSLC1 level evoked obvious proliferation and invasion inhibitions and arrested cell cycle at G0/G1 phase in A431 cells. Moreover, increase of caspase-3 activity mediated by elevated TSLC1 level induced cell apoptosis in A431 cells. Most notably, upregulation of TSLC1 expression reduced the numbers of colony formation and tumorigenicity. Collectively, our results presented herein suggest that TSLC1 as tumor suppressor may play prominent roles in development and progression of CSCC via regulation of different biological processes.

[507]

TÍTULO / TITLE: - Gamma-secretase inhibition attenuates oxaliplatin-induced apoptosis through increased Mcl-1 and/or Bcl-xL in human colon cancer cells.

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

REVISTA / JOURNAL: - Apoptosis. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1007/s10495-013-0883-](#)

[X](#)

AUTORES / AUTHORS: - Timme CR; Gruidl M; Yeatman TJ

INSTITUCIÓN / INSTITUTION: - Department of Experimental Therapeutics, Moffitt Cancer Center, Tampa, FL, USA.

RESUMEN / SUMMARY: - The Notch signaling pathway plays a significant role in differentiation, proliferation, apoptosis, and stem cell processes. It is essential for maintenance of the normal colon crypt and has been implicated in colorectal cancer oncogenesis. Downregulation of the Notch pathway through gamma-secretase inhibitors (GSIs) has been shown to induce apoptosis and enhance response to chemotherapy in a variety of malignancies. In this study, we analyzed the effect of MRK-003 (Merck), a potent inhibitor of gamma-secretase, on oxaliplatin-induced apoptosis in colon cancer. Unexpectedly, gamma-secretase inhibition reduced oxaliplatin-induced apoptosis while GSI treatment alone was shown to have no effect on growth or apoptosis. We determined that the underlying mechanism of action involved an increase in

protein levels of the anti-apoptotic Bcl-2 family members Mcl-1 and/or Bcl-xL which resulted in reduced Bax and Bak activation. Blocking of Mcl-1 and/or Bcl-xL through siRNA or the small molecule inhibitor obatoclax restored the apoptotic potential of cells treated with both oxaliplatin and MRK-003. Moreover, obatoclax synergized with MRK-003 alone to induce apoptosis. Our findings warrant caution when treating colon cancer with the combination of GSIs and chemotherapy, whereas other drug combinations, such as GSIs plus obatoclax, should be explored.

[508]

TÍTULO / TITLE: - A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies.

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

REVISTA / JOURNAL: - Leuk Res. 2013 Sep;37(9):1100-6. doi: 10.1016/j.leukres.2013.04.025. Epub 2013 Jun 5.

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

[1016/j.leukres.2013.04.025](#)

AUTORES / AUTHORS: - Graux C; Sonet A; Maertens J; Duyster J; Greiner J; Chalandon Y; Martinelli G; Hess D; Heim D; Giles FJ; Kelly KR; Gianella-Borradori A; Longerey B; Asatiani E; Rejeb N; Ottmann OG

INSTITUCIÓN / INSTITUTION: - Mont-Godinne University Hospital (UCL), Yvoir, Belgium. Electronic address: carlos.graux@uclouvain.be.

RESUMEN / SUMMARY: - A phase I dose-escalation study of MSC1992371A, an oral aurora kinase inhibitor, was carried out in patients with hematologic malignancies. Patients received escalating doses either on days 1-3 and 8-10 (n=36) or on days 1-6 (n=39) of a 21-day cycle. The maximum tolerated doses were 37 and 28mg/m(2)/day, respectively. Dose-limiting toxicities included severe neutropenia with infection and sepsis, mucositis/stomatitis, and diarrhea. Complete responses occurred in 3 patients. Four disease-specific expansion cohorts then received the dose and schedule dictated by the escalation phase but the study was prematurely discontinued due to hematologic and gastrointestinal toxicity at clinically effective doses.

[509]

TÍTULO / TITLE: - Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jul 12. pii: S0304-3835(13)00512-0. doi: 10.1016/j.canlet.2013.07.007.

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

[1016/j.canlet.2013.07.007](#)

AUTORES / AUTHORS: - Okamoto K; Kodama K; Takase K; Sugi NH; Yamamoto Y; Iwata M; Tsuruoka A

INSTITUCIÓN / INSTITUTION: - Eisai Co., Ltd., Tokodai 5-1-3, Tsukuba, Ibaraki, 300-2635, Japan. Electronic address: k4-okamoto@hbc.eisai.co.jp.

RESUMEN / SUMMARY: - RET gene fusions are recurrent oncogenes identified in thyroid and lung carcinomas. Lenvatinib is a multi-tyrosine kinase inhibitor currently under evaluation in several clinical trials. Here we evaluated lenvatinib in RET gene fusion-driven preclinical models. In cellular assays, lenvatinib inhibited auto-phosphorylation of KIF5B-RET, CCDC6-RET, and NcoA4-RET. Lenvatinib suppressed the growth of CCDC6-RET human thyroid and lung cancer cell lines, and as well, suppressed anchorage-independent growth and tumorigenicity of RET gene fusion-transformed NIH3T3 cells. These results demonstrate that lenvatinib can exert antitumor activity against RET gene fusion-driven tumor models by inhibiting oncogenic RET gene fusion signaling.

[510]

TÍTULO / TITLE: - Osteopontin and splice variant expression level in human malignant glioma: Radiobiologic effects and prognosis after radiotherapy.

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

REVISTA / JOURNAL: - Radiother Oncol. 2013 Jul 25. pii: S0167-8140(13)00315-0. doi: 10.1016/j.radonc.2013.06.036.

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

[1016/j.radonc.2013.06.036](#)

AUTORES / AUTHORS: - Guttler A; Giebler M; Cuno P; Wichmann H; Kessler J; Ostheimer C; Soling A; Strauss C; Illert J; Kappler M; Vordermark D; Bache M

INSTITUCIÓN / INSTITUTION: - Department of Radiotherapy, Martin Luther University Halle-Wittenberg, Germany. Electronic address: antje.hahnel@uk-halle.de.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: We investigated the role of the hypoxia-associated secreted glycoprotein osteopontin (OPN) in the response of malignant glioma to radiotherapy by characterizing OPN and its splice variants in vitro and in patient material. MATERIAL AND METHODS: The effect of siRNA knockdown of OPN splice variants on cellular and radiobiologic behavior was analyzed in U251MG cells using OpnS siRNA (inhibition of all OPN splice variants) and OpnAC siRNA (knockdown only of OPNa and OPNc). OPN and splice variant mRNA levels were quantified in archival material of 41 glioblastoma tumor samples. Plasma OPN was prospectively measured in 33 malignant glioma patients. RESULTS: Inhibition of OPNa and OPNc (OpnAC) reduced clonogenic survival in U251MG cells but did not affect proliferation, migration or apoptosis. Knockdown of all OPN splice variants (OpnS) resulted in an even stronger inhibition of clonogenic survival, while cell proliferation and migration were reduced and rate of apoptosis was increased. Additional irradiation had additive effects with both siRNAs. Plasma OPN increased

continuously in malignant glioma patients and was associated with poor survival. CONCLUSIONS: OPNb is partially able to compensate the effects of OPNa and OPNc knockdown in U251MG cells. High OPN plasma levels at the end of radiotherapy are associated with poor survival.

[511]

TÍTULO / TITLE: - Thyroglobulin as early prognostic marker to predict remission at 18-24 months in differentiated thyroid carcinoma.

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

REVISTA / JOURNAL: - Clin Endocrinol (Oxf). 2013 Jul 4. doi: 10.1111/cen.12282.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cen.12282](#)

AUTORES / AUTHORS: - Gonzalez C; Aulinas A; Colom C; Tundidor D; Mendoza L; Corcoy R; Mato E; Alcantara V; Urgell Rull E; de Leiva A

INSTITUCIÓN / INSTITUTION: - Department of Endocrinology and Nutrition, Hospital Santa Creu i Sant Pau, Barcelona, España; Biomedical Research Networking Centre on Bioengineering, Biomaterials & Nanomedicine: CIBER-BBN- EDUAB-HSP group, Barcelona, España.

RESUMEN / SUMMARY: - INTRODUCTION: Thyroglobulin (Tg), the most common marker to determine remission of differentiated thyroid carcinoma (DTC), can take 18 months or longer to be undetectable. We hypothesized that Tg stimulated after surgery and immediately before radioiodine treatment (baseline-stimulated Tg) could be a good predictor of remission at 18-24 months. The aim of this study was to evaluate the role of baseline-stimulated Tg as early prognostic marker of DTC. PATIENTS AND METHODS: Retrospective study of 133 patients with DTC from 1998 to 2010 (age at diagnosis 47.4 +/- 16.8, follow-up 5.09 +/- 3.2 years). Initial subset analysis was performed after excluding patients with positive TgAb, who were later included in the second. Baseline-stimulated Tg was divided into tertiles. Multivariate logistic regression analysis included baseline Tg and other known prognostic markers and receiver operating characteristic (ROC) curve to identify the best cut-off level of baseline Tg were performed. RESULTS: Baseline-stimulated Tg in the highest tertile was the only predictive variable of persistence of disease at 18-24 months in the initial analysis (OR 45.3, P < 0.01). In the second analysis, the predictive variables were baseline-stimulated Tg (OR 39.6, P < 0.001), presence of TgAb (OR 23.4, P < 0.005) and uptake outside of the thyroid bed post-treatment whole body scan (WBS; OR 5.3, P < 0.05) were predictive of persistence of disease. The ROC curve showed that baseline-stimulated Tg below 8.55 mug/l identified 95% of disease-free patients at 18-24 months after initial treatment. CONCLUSIONS: Baseline-stimulated Tg is a good predictor of remission of disease at 18-24 months after initial treatment and could be a useful marker to stratify risk immediately after surgery.

[512]

TÍTULO / TITLE: - Relationship between glutathione S-transferase P1 (GSTP1), X-ray repair cross complementing group 1 (XRCC1) and 5,10-methylenetetrahydrofolate reductase (5,10-MTHFR) gene polymorphisms and response to chemotherapy in advanced gastric cancer.

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

REVISTA / JOURNAL: - Onkologie. 2013;36(6):335-40. doi: 10.1159/000351260. Epub 2013 May 21.

●● Enlace al texto completo (gratis o de pago) [1159/000351260](#)

AUTORES / AUTHORS: - Ji M; Xu B; Jiang JT; Wu J; Li XD; Zhao WQ; Zhang HY; Zhou WJ; Wu CP

INSTITUCIÓN / INSTITUTION: - Department of Oncology, The Third Affiliated Hospital of Soochow University, Changzhou, China.

RESUMEN / SUMMARY: - BACKGROUND: Our study aimed to investigate the relationship between glutathione S-transferase P1 (GSTP1), 5,10-methylenetetrahydrofolate reductase (5,10-MTHFR) and X-ray repair cross complementing group 1 (XRCC1) gene polymorphisms and the response to chemotherapy in advanced gastric cancer. PATIENTS AND METHODS: 59 cases of advanced gastric cancer were enrolled. All patients were treated with the DCF regimen comprising docetaxel, cisplatin, and 5-fluorouracil. All patients' genotypes regarding GSTP1, XRCC1, and 5,10-MTHFR were analyzed by polymerase chain reaction/ligase detection reaction (PCR-LDR). RESULTS: There were 15 (25.42%) cases of G/G genotype, 21 (35.59%) of G/A genotype, and 23 (38.98%) of A/A genotype for GSTP1, 16 (27.12%) cases of A/A genotype, 18 (30.51%) of G/A genotype, and 25 (42.37%) of G/G genotype for XRCC1, and 21 (35.59%) cases of C/C genotype, 22 (37.29%) of C/T genotype, and 16 (27.12%) of T/T genotype for 5,10-MTHFR. After 2 cycles of chemotherapy, there were 4 cases of complete remission, 14 of partial remission, 19 of stable disease, and 22 of advanced disease, with a total effective rate of 30.51%. Better survival was shown for GSTP1 G/G genotype, XRCC1 A/A genotype, and 5,10-MTHFR T/T genotype ($p < 0.05$). CONCLUSION: The gene polymorphisms of GSTP1 G/G, XRCC1 A/A, and 5,10-MTHFR T/T have clinical value for predicting the response to the DCF regimen for advanced gastric cancer.

[513]

TÍTULO / TITLE: - GPR48, a poor prognostic factor, promotes tumor metastasis and activates beta-catenin/TCF signaling in colorectal cancer.

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

REVISTA / JOURNAL: - Carcinogenesis. 2013 Aug 3.

●● Enlace al texto completo (gratis o de pago) [1093/carcin/bgt229](#)

AUTORES / AUTHORS: - Wu J; Xie N; Xie K; Zeng J; Cheng L; Lei Y; Liu Y; Song L; Dong D; Chen Y; Zeng R; Nice EC; Huang C; Wei Y

INSTITUCIÓN / INSTITUTION: - The State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, P. R. China.

RESUMEN / SUMMARY: - G-protein-coupled receptor 48 (GPR48) is an orphan receptor belonging to the G-protein-coupled receptors family, which plays an important role in the development of various organs and cancer development and progression such as gastric cancer and colorectal cancer (CRC). However, the prognostic value of GPR48 expression in patients with CRC has not been reported. In this study, we observed that GPR48 was overexpressed in primary CRC and metastatic lymph nodes and closely correlated with tumor invasion and metastasis. Multivariate analysis indicated that high GPR48 expression was a poor prognostic factor for overall survival in CRC patients. In vitro and in vivo assays demonstrated that enforced expression of GPR48 contributed to enhance migration and invasion of cancer cells and tumor metastasis. In addition, we found that GPR48 increased nuclear beta-catenin accumulation, T-cell factor 4 (TCF4) transcription activity, and expression of its target genes including Cyclin D1 and c-Myc in CRC cells. Correlation analysis showed that GPR48 expression in CRC tissues was positively associated with beta-catenin expression. Upregulation of GPR48 resulted in increased phosphorylation of glycogen synthase kinase 3beta, Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) in CRC cells, while inhibition of PI3K/Akt and mitogen-activated protein kinase /ERK1/2 pathways was sufficient to abolish the effect of GPR48 on beta-catenin/TCF signaling. Taken together, GPR48 could serve as both a prognostic biomarker and a therapeutic target for resectable CRC patients.

[514]

TÍTULO / TITLE: - Soluble ICAM-1 levels in small-cell lung cancer: prognostic value for survival and predictive significance for response during chemotherapy.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):662. doi: 10.1007/s12032-013-0662-0. Epub 2013 Jul 25.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0662-](#)

[0](#)

AUTORES / AUTHORS: - Kotteas EA; Gkiozos I; Tsagkouli S; Bastas A; Ntanos I; Saif MW; Syrigos KN

INSTITUCIÓN / INSTITUTION: - Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, 152, Mesogeion Av., 115 27, Athens, Greece.

RESUMEN / SUMMARY: - Intercellular adhesion molecule-1 (ICAM-1) is an adhesion molecule, member of the immunoglobulin gene superfamily that seems to participate in the evolution of the metastatic process. We investigated the significance of baseline soluble ICAM-1 levels on the outcome of patients with small-cell lung cancer and whether soluble ICAM-1 is a predictive marker

for objective response during and after chemotherapy in patients with small-cell lung cancer. Fifty patients with recently diagnosed small-cell lung cancer, as well as 27 healthy smokers, were enrolled. Blood samples were collected at the time of diagnosis, during and at the end of chemotherapy. Data were correlated with the characteristics of the patients and survival as well as with ICAM-1 predictive role for objective response. Statistical significant values of baseline soluble ICAM between patients and controls ($p < 0.001$) were observed. Multivariate analysis revealed an elevated risk of death of 9 % in the first year after diagnosis for every 10 units of increased soluble ICAM-1 at the baseline ($p = 0.046$). Performance status and disease stage were also independent prognostic factors. Patients with extensive disease who achieved an objective response during chemotherapy showed a significant decrease (25.8 %) in their soluble ICAM-1 levels compared with baseline levels ($p = 0.001$). Alongside performance status and disease stage, baseline soluble ICAM-1 could be evaluated as an additional prognostic factor in patients with small-cell lung cancer. Also, a possible role for soluble ICAM-1 may exist as a predictive marker for objective response during chemotherapy for patients with extensive disease ($p = 0.001$).

[515]

TÍTULO / TITLE: - Prostate-Specific Antigen Kinetics under Androgen Deprivation Therapy and Prostate Cancer Prognosis.

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

REVISTA / JOURNAL: - Urol Int. 2013;91(1):38-48. doi: 10.1159/000345939. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [1159/000345939](#)

AUTORES / AUTHORS: - Zhang LM; Jiang HW; Tong SJ; Zhu HQ; Liu J; Ding Q

INSTITUCIÓN / INSTITUTION: - Department of Urology, Huashan Hospital, Fudan University, Shanghai, P.R. China.

RESUMEN / SUMMARY: - Objectives: To compare the difference in characteristics of post-treatment prostate-specific antigen (PSA) kinetics among respective patients and their influence on disease prognosis. Methods: A cohort of totally 332 eligible patients with histologically confirmed and hormonally naive prostate cancer, identified from the patients' database of Huashan Hospital, all received combined androgen deprivation therapy including bilateral orchiectomy or luteinizing hormone-releasing hormone antagonists with the oral administration of flutamide 250 mg t.i.d. All patients had their serum PSA level tested at least every 3 months in the first 2 years and at least once a half year from the third year on. PSA nadir, time to PSA nadir (TTPN), PSA normalization (<4 ng/ml), undetectable PSA level (<0.2 ng/ml), biochemical failure, overall survival and cancer-specific survival were analyzed. Results: PSA normalization, TTPN, and reaching the undetectable PSA level perhaps were the independent risk factors for predicting the three types of prognosis. Probably the best cut-off of PSA

nadir was 0.2 ng/ml (sensitivity 65.7%, specificity 80.6%) and the best cut-off of TTPN was 10 months (sensitivity 71.6%, specificity 63.9%). Conclusions: These results implied that a lower level of PSA nadir and longer TTPN can predict a better disease prognosis.

[516]

TÍTULO / TITLE: - Changes in signaling pathways induced by vandetanib in a human medullary thyroid carcinoma model, as analyzed by Reverse Phase Protein Array.

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

REVISTA / JOURNAL: - Thyroid. 2013 Jul 3.

●● [Enlace al texto completo \(gratis o de pago\) 1089/thy.2012.0224](#)

AUTORES / AUTHORS: - Broutin S; Commo F; De Koning L; Marty-Prouvost B; Lacroix L; Talbot M; Caillou B; Dubois T; Ryan AJ; Dupuy C; Schlumberger M; Bidart JM

INSTITUCIÓN / INSTITUTION: - Institut Gustave-Roussy, CNRS UMR8200, Villejuif, France ; broutin@igr.fr.

RESUMEN / SUMMARY: - **Background:** Medullary thyroid carcinoma (MTC) is a rare tumor that is due to activating mutations in the proto-oncogene RET. Vandetanib, a tyrosine-kinase inhibitor, has been recently approved to treat adult patients with metastatic MTC. The aim of this study was to investigate changes in signaling pathways induced by vandetanib treatment in preclinical MTC models, using the reverse-phase protein array method (RPPA). **Methods:** The human TT cell line was used to assess *in vitro* and *in vivo* activity of vandetanib. Protein extracts from TT cells or TT xenografted mice, treated by increasing concentrations of vandetanib for different periods of time, were probed with a set of 12 antibodies representing major signaling pathways, using RPPA. Results were validated using two distinct protein detection methods, western-immunoblotting and immunohistochemistry. **Results:** Vandetanib displays antiproliferative and antiangiogenic activities and inhibits RET auto-phosphorylation. MAPK and AKT pathways were the two major signaling pathways inhibited by vandetanib. Interestingly, phosphorylated levels of NFkappaB-p65 were significantly increased by vandetanib. Comparable results were obtained in both the *in vitro* and *in vivo* approaches as well as for the protein detection methods, although some discrepancies were observed between RPPA and western-immunoblotting. **Conclusions:** Results confirmed the reliability and the utility of RPPA for screening global changes induced in signaling pathways by kinase inhibitors. MAPK and AKT were identified as the main pathways involved in vandetanib response in MTC models. Our results also suggest alternative routes for controlling the disease and provide a rationale for the development of

therapeutic combinations based on the comprehensive identification of molecular events induced by inhibitors.

[517]

TÍTULO / TITLE: - Nuclear Expression of Glioma-Associated Oncogene Homolog 1 and Nuclear Factor-kappaB Is Associated with a Poor Prognosis of Pancreatic Cancer.

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

REVISTA / JOURNAL: - Oncology. 2013 Jul 16;85(2):86-94.

●● Enlace al texto completo (gratis o de pago) [1159/000353452](#)

AUTORES / AUTHORS: - Yang SH; Hsu CH; Lee JC; Tien YW; Kuo SH; Cheng AL

INSTITUCIÓN / INSTITUTION: - Department of Oncology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.

RESUMEN / SUMMARY: - Objective: We investigated the association of the hedgehog pathway with nuclear factor (NF)-kappaB and clinical outcomes in pancreatic cancer patients. Methods: We analyzed tissue samples for the expression of NF-kappaB (RelA/p65), sonic hedgehog (Shh) and glioma-associated oncogene homolog 1 (Gli1) by immunohistochemistry and investigated their expression in association with clinical outcomes. Results: Eighty-one patients with pancreatic cancer were investigated. Expression of Shh and nuclear expression of Gli1 and NF-kappaB were found in 63 of 66 (96%), 28 of 68 (41%) and 22 of 68 cases (32%), respectively. Nuclear Gli1 expression was closely associated with nuclear expression of NF-kappaB ($p < 0.001$). Patients with nuclear Gli1 had significantly worse prognoses than those without (median survival 7.9 vs. 13.9 months; $p = 0.009$). Similarly, patients with nuclear expression of NF-kappaB had shorter overall survival than those with negative or cytoplasmic expression of NF-kappaB (median survival 5.5 vs. 13.9 months; $p < 0.001$). Shh expression had no prognostic significance. In the multivariate analysis, NF-kappaB nuclear expression was closely associated with unfavorable overall survival ($p = 0.02$). Conclusion: Our results indicate that nuclear expression of Gli1 or NF-kappaB is a strong predictor of poor prognosis in pancreatic cancer. Additional investigation of the biologic significance of this association is warranted. © 2013 S. Karger AG, Basel.

[518]

TÍTULO / TITLE: - Tumour morphology predicts PALB2 germline mutation status.

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

REVISTA / JOURNAL: - Br J Cancer. 2013 Jul 9;109(1):154-63. doi: 10.1038/bjc.2013.295. Epub 2013 Jun 20.

●● Enlace al texto completo (gratis o de pago) [1038/bjc.2013.295](#)

AUTORES / AUTHORS: - Teo ZL; Provenzano E; Dite GS; Park DJ; Apicella C; Sawyer SD; James PA; Mitchell G; Trainer AH; Lindeman GJ; Shackleton K; Ciciarelli L; Buys SS; Andrulis IL; Mulligan AM; Glendon G; John EM; Terry MB; Daly M; Odefrey FA; Nguyen-Dumont T; Giles GG; Dowty JG; Winship I; Goldgar DE; Hopper JL; Southey MC

INSTITUCIÓN / INSTITUTION: - Genetic Epidemiology Laboratory, The University of Melbourne, Melbourne, Victoria 3010, Australia.

RESUMEN / SUMMARY: - Background: Population-based studies of breast cancer have estimated that at least some PALB2 mutations are associated with high breast cancer risk. For women carrying PALB2 mutations, knowing their carrier status could be useful in directing them towards effective cancer risk management and therapeutic strategies. We sought to determine whether morphological features of breast tumours can predict PALB2 germline mutation status. Methods: Systematic pathology review was conducted on breast tumours from 28 female carriers of PALB2 mutations (non-carriers of other known high-risk mutations, recruited through various resources with varying ascertainment) and on breast tumours from a population-based sample of 828 Australian women diagnosed before the age of 60 years (which included 40 BRCA1 and 18 BRCA2 mutation carriers). Tumour morphological features of the 28 PALB2 mutation carriers were compared with those of 770 women without high-risk mutations. Results: Tumours arising in PALB2 mutation carriers were associated with minimal sclerosis (odds ratio (OR)=19.7; 95% confidence interval (CI)=6.0-64.6; $P=5 \times 10^{-7}$). Minimal sclerosis was also a feature that distinguished PALB2 mutation carriers from BRCA1 ($P=0.05$) and BRCA2 ($P=0.04$) mutation carriers. Conclusion: This study identified minimal sclerosis to be a predictor of germline PALB2 mutation status. Morphological review can therefore facilitate the identification of women most likely to carry mutations in PALB2.

[519]

TÍTULO / TITLE: - Vitamin K4 induces tumor cytotoxicity in human prostate carcinoma PC-3 cells via the mitochondria-related apoptotic pathway.

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

REVISTA / JOURNAL: - Pharmazie. 2013 Jun;68(6):442-8.

AUTORES / AUTHORS: - Jiang Y; Yang J; Yang C; Meng F; Zhou Y; Yu B; Khan M; Yang H

INSTITUCIÓN / INSTITUTION: - School of Life Sciences, Liaoning Provincial Key Laboratory of Biotechnology and Drug Discovery, Liaoning Normal University, Dalian, PR China.

RESUMEN / SUMMARY: - Vitamin K4 (VK4) is a synthetic hydrophilic menadione compound, which is clinically used as hemostasis medicine. It has been reported that several vitamin Ks had inhibitory effects on various cancer cells. However, there is no report about VK4s anticancer activity. The goal of this study was to investigate the inhibitory effect of VK4 on human prostate PC-3

cells and the mechanisms involved. We found that VK4 dose-dependently inhibited cell proliferation in PC-3 cells with an IC50 value of about 20.94 microM. Hoechst 33258 Staining results showed that VK4 caused DNA fragmentation in PC-3 cells. PI staining results indicated that VK4-induced PC-3 cell cycle arrest at the S phase. Further mechanistic studies revealed that VK4-mediated induction of apoptosis in PC-3 cell is associated with disruption of mitochondrial membrane potential, down-regulation of Bcl-2, and up-regulation of Bax, release of cytochrome c from mitochondria, and activation of caspase-3 and PARP. Thus, VK4 might be useful in prostate cancer chemotherapy.

[520]

TÍTULO / TITLE: - A new anti-cancer strategy of damaging mitochondria by pro-apoptotic peptide functionalized gold nanoparticles.

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

REVISTA / JOURNAL: - Chem Commun (Camb). 2013 Jun 20;49(57):6403-5. doi: 10.1039/c3cc43283a.

●● Enlace al texto completo (gratis o de pago) [1039/c3cc43283a](#)

AUTORES / AUTHORS: - Chen WH; Chen JX; Cheng H; Chen CS; Yang J; Xu XD; Wang Y; Zhuo RX; Zhang XZ

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Biomedical Polymers of Ministry of Education & Department of Chemistry, Wuhan University, Wuhan 430072, P. R. China. xz-zhang@whu.edu.cn.

RESUMEN / SUMMARY: - Gold nanoparticles functionalized with pro-apoptotic peptide (PAP-AuNPs) were fabricated, which were able to lead to programmed cell-death by damaging mitochondria.

[521]

TÍTULO / TITLE: - Intrathecal liposomal cytarabine and leptomeningeal medulloblastoma relapse: a valuable therapeutic option.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3515-8.

AUTORES / AUTHORS: - Mastronuzzi A; Del Bufalo F; Iacono A; Secco DE; Serra A; Colafati GS; DE Ioris MA; Corsetti T

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology and Stem Cell Transplantation, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio, 4-00165, Rome, Italy. angela.mastronuzzi@opbg.net.

RESUMEN / SUMMARY: - BACKGROUND: Relapsed medulloblastoma (MB) is a highly lethal disease, requiring for new effective treatment strategies. Intrathecal (IT) therapy both for de novo or relapsed brain tumors with meningeal metastasis is rarely used in first line and relapse protocols. PATIENTS AND METHODS: We report on three cases of children with relapsed MB treated with IT liposomal cytarabine administered after mild sedation every 15 days.

RESULTS: The treatment was well-tolerated in all patients, achieving a prolonged progression-free survival (4-11 months) with a good quality of life.
CONCLUSION: This experience suggests the need for a phase II trial in brain embryonal tumors with leptomeningeal metastasis to better evaluate the efficacy of IT liposomal cytarabine.

[522]

TÍTULO / TITLE: - Histologic prognostic factors associated with chromosomal imbalances in a contemporary series of 89 clear cell renal cell carcinomas.

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

REVISTA / JOURNAL: - Hum Pathol. 2013 Jun 24. pii: S0046-8177(13)00149-4. doi: 10.1016/j.humpath.2013.03.018.

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

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

AUTORES / AUTHORS: - Dagher J; Dugay F; Verhoest G; Cabillic F; Jaillard S; Henry C; Arlot-Bonnemains Y; Bensalah K; Oger E; Vigneau C; Rioux-Leclercq N; Belaud-Rotureau MA

INSTITUCIÓN / INSTITUTION: - Service d'Anatomie et Cytologie Pathologiques, CHU de Rennes, 35000 Rennes, France.

RESUMEN / SUMMARY: - Clear cell renal cell carcinoma (ccRCC) is the most common type of renal cancer. The aim of this study was to define specific chromosomal imbalances in ccRCC that could be related to clinical or histologic prognostic factors. Tumors and karyotypes of 89 patients who underwent nephrectomy for ccRCC were analyzed from April 2009 to July 2012. The mean number of chromosomal aberrations was significantly higher (7.8; $P < .05$) in Fuhrman grade 4 (F4) than in F3 (4) and F2 (3.4) cases. The results were similar, considering separately the mean number of chromosomal losses and gains. The F4 cases had a distinct pattern with more frequent losses of chromosomes 9, 13, 14, 18, 21, 22, and Y and gains of chromosome 20. Necrosis was associated with losses of chromosomes 7, 9, 18, and 22; sarcomatoid component, losses of chromosomes 7, 9, and 14 and gains of 20; and T stage, losses of chromosomes 18 and Y. After multivariate analysis, renal fat invasion, renal vein emboli, and microscopic vascular invasion were, respectively, associated with losses of chromosomes 13 and Y, loss of chromosome 13, and loss of chromosome 14 and gains of chromosomes 7 and 20. F4 was independently associated with losses of chromosomes 9 and Y; sarcomatoid component, loss of chromosome 9 and gain of 20; necrosis, loss of chromosome 18; and T stage, loss of chromosome Y. These chromosomal imbalances can be detected routinely by karyotype or fluorescence in situ hybridization analyses to stratify patients for risk of progression.

[523]

TÍTULO / TITLE: - Phosphorylated insulin-like growth factor-1 receptor (pIGF1R) is a poor prognostic factor in brain metastases from lung adenocarcinomas.

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

REVISTA / JOURNAL: - J Neurooncol. 2013 Jul 2.

●● Enlace al texto completo (gratis o de pago) [1007/s11060-013-1194-](#)

[3](#)

AUTORES / AUTHORS: - Wu PF; Huang WC; Yang JC; Lu YS; Shih JY; Wu SG; Lin CH; Cheng AL

INSTITUCIÓN / INSTITUTION: - National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei, 100, Taiwan.

RESUMEN / SUMMARY: - A greater understanding of brain metastases is imperative for developing novel therapeutic strategies. Our previous study showed that insulin-like growth factor (IGF) signaling pathway was activated in brain-tropic cancer cells. In this study, we investigated the clinical relevance of activated (phosphorylated) IGF-1 receptor (pIGF1R) expression in brain metastases originating from lung adenocarcinomas. All pathologically confirmed brain metastases from lung adenocarcinomas, with available archived specimens from January 1998 to December 2009 at National Taiwan University Hospital, were assessed immunohistochemically for pIGF1R expression using H-score criteria. A median H-score was used as a cutoff point to define high or low pIGF1R expression. The mutation status in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) was examined using direct sequencing. The prognostic significance of pIGF1R expression, its correlations with clinicopathological characteristics, and EGFR status were evaluated. In the 86 cases, high membranous/cytoplasmic pIGF1R expression in brain metastases correlated with a shorter median survival (10.8 vs 27.8 mo, $P = 0.003$). This correlation was more significant in patients with EGFR mutations [hazard ratio (HR) 2.38, 95 % confidence interval (CI) 1.19-4.77 for EGFR mutations; HR 1.99, 95 % CI 0.95-4.15 for EGFR wild type] and remained statistically significant in multivariate analysis after adjusting for the effects of other potential prognostic factors, including the graded prognostic assessment score, solitary brain metastasis, extracranial metastatic status, EGFR mutations, and treatment using EGFR tyrosine kinase inhibitors. Although we also identified nuclear pIGF1R expression, this result was prognostically non-significant. Our study results showed that high membranous/cytoplasmic pIGF1R expression in brain metastases was a poor prognostic factor, more significantly in patients with EGFR mutations than in those with wild-type EGFRs.

[524]

TÍTULO / TITLE: - Genistein-induced G2/M cell cycle arrest of human intestinal colon cancer Caco-2 cells is associated with Cyclin B1 and Chk2 down-regulation.

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

REVISTA / JOURNAL: - Cytotechnology. 2013 Jun 21.

●● Enlace al texto completo (gratis o de pago) [1007/s10616-013-9592-](#)

[0](#)

AUTORES / AUTHORS: - Han J; Kurita Y; Isoda H

INSTITUCIÓN / INSTITUTION: - Graduate School of Life and Environmental Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8572, Japan, han.junkyu.gn@u.tsukuba.ac.jp.

RESUMEN / SUMMARY: - Genistein is an isoflavonic phyto-oestrogen contained in soya beans. It is thought to display anti-cancer effects. This study was designed to investigate its effect on human intestinal colon cancer Caco-2 cells. MTT assay, flow cytometric analysis and western blotting were used to investigate the effect of genistein on cell proliferation, cell cycle progression and protein alterations of selected cell cycle-related proteins in Caco-2 cells. Our results showed that genistein and daidzein significantly suppressed cell proliferation. Genistein treatment was demonstrated to modulate cell cycle distribution through accumulation of cells at G2/M phase, with a significant decreasing effect of Cyclin B1 and Serine/threonine-protein kinase 2 (Chk2) proteins expression. However, daidzein did not alter the cell cycle progression in Caco-2 cells. All these observations strongly indicate that genistein has anti-proliferative effect in human intestinal colon cancer Caco-2 cells through the down-regulation of cell cycle check point proteins, Cyclin B1 and Chk2.

[525]

TÍTULO / TITLE: - Establishment of a Predictive Genetic Model for Estimating Chemotherapy Sensitivity of Colorectal Cancer with Synchronous Liver Metastasis.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 May 30.

●● Enlace al texto completo (gratis o de pago) [1089/cbr.2012.1431](#)

AUTORES / AUTHORS: - Lu X; Pan J; Li S; Shen S; Chi P; Lin H; Huang Y; Xu Z; Huang S

INSTITUCIÓN / INSTITUTION: - 1 Department of Colorectal Surgery, Union Hospital, Fujian Medical University, Fuzhou, China.

RESUMEN / SUMMARY: - Abstract Objective: We examined the whole genome expression profile in advanced colorectal cancer (ACC) patients who had received FOLFOX4 chemotherapy to establish a genetic biomarker model predicting chemotherapy sensitivity. Methods: Eligible ACC patients were divided into two groups, based on postchemotherapy evaluation results: specifically, the sensitive group (experimental group) and the resistant group

(control group). The genome expression profiles of colorectal cancer tissues were examined using DNA microarray analysis, and differential gene expression was identified using a significance analysis of the microarray. The probe signal log ratios were used to produce the area-under-the-curve, sensitivity, and specificity for candidate genes. Genes exhibiting differential expression and significant predictive power were used to simulate a genetic model for estimating chemotherapy sensitivity. Results: Totally, 30 ACC patients were eligible for the study, 13 assigned to the experimental group and 17 to the control group. In total, 30 genes showing significant differential expression were identified. Seven candidate genes (NKX2-3, FXYD6, TGFB111, ACTG2, ANPEP, HOXB8, and KLK11), which exhibited positive or negative correlations, were incorporated into a genetic model, with an overall accurate predication rate of 93.3%. Conclusions: The predictive model involving the seven genes listed had high accuracy in estimating chemotherapy sensitivity to the FOLFOX4 regimen.

[526]

TÍTULO / TITLE: - Fibroblast growth factor receptor 1 (FGFR1) copy number is an independent prognostic factor in non-small cell lung cancer.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Jun 24. pii: S0169-5002(13)00247-X. doi: 10.1016/j.lungcan.2013.05.015.

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

[1016/j.lungcan.2013.05.015](#)

AUTORES / AUTHORS: - Tran TN; Selinger CI; Kohonen-Corish MR; McCaughan BC; Kennedy CW; O'Toole SA; Cooper WA

INSTITUCIÓN / INSTITUTION: - Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia.

RESUMEN / SUMMARY: - Fibroblast growth factor receptor 1 (FGFR1) is an oncogene that can potentially be targeted by tyrosine kinase inhibitors. We aimed to investigate the prevalence and prognostic significance of alterations in FGFR1 copy number in non-small cell lung cancer (NSCLC). FGFR1 status was evaluated by chromogenic silver in situ hybridisation (ISH) in tissue microarray sections from a retrospective cohort of 304 surgically resected NSCLCs and results were correlated with the clinicopathological features and overall survival. High FGFR1 gene copy number (amplification or high-level polysomy) was significantly more frequent in squamous cell carcinomas (SCC) (24.8%) and large cell carcinomas (LCC) (25%) compared to adenocarcinomas (11.3%) (p=0.01 and p=0.03 respectively). Among NSCLC there was no significant correlation between FGFR1-positive status and other clinicopathological features including age, gender, smoking history, tumour size, lymph node status, stage, grade, vascular, lymphatic or perineural invasion. FGFR1-positive patients showed a tendency to longer overall survival in univariate analysis

($p=0.14$). Multivariate survival analysis using Cox regression model confirmed FGFR1-positive patients had a significant reduction in the risk of death compared to FGFR1-negative patients (HR 0.6; $p=0.02$). High FGFR1 gene copy number is a common finding in SCC and LCC and is an independent favourable prognostic factor.

[527]

TÍTULO / TITLE: - Induction of human leukemia U937 cell apoptosis by an ethanol extract of *Dendropanax morbifera* Lev. through the caspase-dependent pathway.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 19. doi: 10.3892/or.2013.2542.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2542](#)

AUTORES / AUTHORS: - Lee JW; Park C; Han MH; Hong SH; Lee TK; Lee SH; Kim GY; Choi YH

INSTITUCIÓN / INSTITUTION: - Bunpo School, Nam-gu, Busan 608-832, Republic of Korea.

RESUMEN / SUMMARY: - *Dendropanax morbifera* Leveille is found throughout southwestern Korea, and has been used in traditional medicine for various diseases, such as migraine headache, infectious diseases, skin diseases and dysmenorrhea. However, the molecular mechanisms of *D. morbifera* concerning its biochemical actions in cancer have not yet been clearly elucidated. In the present study, we investigated the pro-apoptotic effects of an ethanol extract of *D. morbifera* stem bark (EEDM) on human leukemia U937 cells. EEDM markedly inhibited the growth of U937 cells by decreasing cell proliferation and inducing apoptosis. EEDM-induced apoptosis in U937 cells was associated with the upregulation of death receptor-related protein levels and downregulation of anti-apoptotic IAP family proteins. The increase in apoptosis was also associated with proteolytic activation of caspase-8, -9 and -3, inhibition of antiapoptotic Bcl-2 and Bcl-xL expression, Bid cleavage, and loss of MMP suggesting that apoptosis of U937 cells induced by EEDM was through the extrinsic and intrinsic pathways. However, a pan-caspase inhibitor, z-VED-fmk, significantly inhibited EEDM-induced U937 cell apoptosis indicating that the caspases were key regulators of apoptosis in response to EEDM in U937 cells. Our data suggest that *D. morbifera* may be a potential anticancer agent for cancer treatment.

[528]

TÍTULO / TITLE: - Loss of heterozygosity at 13q13 and 14q32 predicts BRCA2 inactivation in luminal breast carcinomas.

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

REVISTA / JOURNAL: - Int J Cancer. 2013 Jun 10. doi: 10.1002/ijc.28315.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28315](https://doi.org/10.1002/ijc.28315)

AUTORES / AUTHORS: - Pecuchet N; Popova T; Manie E; Lucchesi C; Battistella A; Vincent-Salomon A; Caux-Moncoutier V; Bollet M; Sigal-Zafrani B; Sastre-Garau X; Stoppa-Lyonnet D; Stern MH

INSTITUCIÓN / INSTITUTION: - Institut Curie, Centre de Recherche, Paris, France; INSERM U830, Paris, France; Department of Tumor Biology, Institut Curie, Paris, France.

RESUMEN / SUMMARY: - BRCA2 is the major high-penetrance predisposition gene for luminal (estrogen receptor [ER] positive) breast cancers. However, many BRCA2 mutant carriers lack family history of breast/ovarian cancers and do not benefit from genetic testing. Specific genomic features associated with BRCA2 inactivation in tumors could help identify patients for whom a genetic test for BRCA2 may be proposed. A series of ER-positive invasive ductal carcinomas (IDCs) including 30 carriers of BRCA2 mutations and 215 control cases was studied by single-nucleotide polymorphism (SNP) arrays. Cases and controls were stratified by grade and HER2 status. Independently, 7 BRCA2 and 51 control cases were used for validation. Absolute copy number and Loss of heterozygosity (LOH) profiles were obtained from SNP arrays by the genome alteration print (GAP) method. BRCA2 tumors were observed to display a discriminatively greater number of chromosomal breaks calculated after filtering out and smoothing <3 Mb variations. This argues for a BRCA2-associated genomic instability responsible for long-segment aberrations. Co-occurrence of two genomic features-LOH of 13q13 and 14q32-was found to predict BRCA2 status with 90% of sensitivity and 87% of specificity in discovery series of high-grade HER2-negative IDCs and 100% of sensitivity and 88% of specificity in an independent series of 58 IDCs. Estimated positive predictive value was 17.2% (confidence interval: 6.7-33.5) in the whole series. In conclusion, the simplified BRCA2 classifier based on the co-occurrence of LOH at 13q13 and 14q32 could provide an indication to test for BRCA2 mutation in patients with ER-positive IDC.

[529]

TÍTULO / TITLE: - Ursolic acid promotes cancer cell death by inducing Atg5-dependent autophagy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](https://doi.org/10.1002/ijc.28301)

REVISTA / JOURNAL: - Int J Cancer. 2013 Jun 4. doi: 10.1002/ijc.28301.

●● Enlace al texto completo (gratis o de pago) [1002/ijc.28301](https://doi.org/10.1002/ijc.28301)

AUTORES / AUTHORS: - Leng S; Hao Y; Du D; Xie S; Hong L; Gu H; Zhu X; Zhang J; Fan D; Kung HF

INSTITUCIÓN / INSTITUTION: - Department of Human Anatomy, Guangzhou Medical University, Guangzhou, Guangdong, People's Republic of China.

RESUMEN / SUMMARY: - Ursolic acid (UA) has been reported to possess anticancer activities. Although some of the anticancer activities of UA have

been explained by its apoptosis-inducing properties, the mechanisms underlying its anticancer actions are largely unknown. We have found that UA-activated autophagy induced cytotoxicity and reduced tumor growth of cervical cancer cells TC-1 in a concentration-dependent manner. UA did not induce apoptosis of TC-1 cells in vitro as determined by annexin V/propidium iodide staining, DNA fragmentation, and Western blot analysis of the apoptosis-related proteins. We found that UA increased punctate staining of light chain 3 (LC3), which is an autophagy marker. LC3II, the processed form of LC3I which is formed during the formation of double membranes, was induced by UA treatment. These results were further confirmed by transmission electron microscopy. Wortmannin, an inhibitor of autophagy, and a small interfering RNA (siRNA) for autophagy-related genes (Atg5) reduced LC3II and simultaneously increased the survival of TC-1 cells treated with UA. We also found that LC3II was significantly reduced and that survival was increased in Atg5^{-/-} mouse embryonic fibroblast (MEF) cells compared to Atg5^{+/+} MEF cells under UA treatment. However, silencing BECN1 by siRNA affected neither the expression of LC3II nor the survival of TC-1 cells under UA treatment. These results suggest that autophagy is a major mechanism by which UA kills TC-1 cells. It is Atg5 rather than BECN1 that plays a crucial role in UA-induced autophagic cell death in TC-1 cells. The activation of autophagy by UA may become a potential cancer therapeutic strategy complementing the apoptosis-based therapies. Furthermore, regulation of Atg5 may improve the efficacy of UA in cancer treatment.

[530]

TÍTULO / TITLE: - Identification of Hepatoma-Derived Growth Factor as a Potential Prognostic and Diagnostic Marker for Extrahepatic Cholangiocarcinoma.

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

REVISTA / JOURNAL: - World J Surg. 2013 Jun 21.

●● Enlace al texto completo (gratis o de pago) [1007/s00268-013-2132-](http://1007/s00268-013-2132-4)

[4](#)

AUTORES / AUTHORS: - Han Y; Zhang W; Liu Y

INSTITUCIÓN / INSTITUTION: - Department of Nursing, Binzhou Vocational College, Binzhou, People's Republic of China.

RESUMEN / SUMMARY: - BACKGROUND: Hepatoma-derived growth factor (HDGF) has been reported to play a pivotal role in the development and progression of several tumors. The aim of the present study was to analyze whether HDGF is a potential prognostic and diagnostic marker for extrahepatic cholangiocarcinoma (EHCC). METHODS: The immunostaining of HDGF was analyzed by immunohistochemistry for 65 pathologically confirmed EHCC, and its correlation with clinicopathologic factors and prognosis was investigated. Meanwhile, to evaluate the diagnostic value of HDGF, an enzyme-linked

immunosorbent assay (ELISA) was performed to measure HDGF levels in the serum samples of 83 EHCC patients and 51 healthy controls. RESULTS: Positive expression of HDGF was detected in 30 (46.2 %) patients with EHCC and correlated with poor tumor differentiation ($P = 0.024$). Univariate analysis showed that the positive HDGF expression group had a significantly poorer survival rate than the negative HDGF expression group did ($P < 0.001$). Multivariate analysis demonstrated that HDGF expression and N stage were independent prognostic factors. The mean serum HDGF level in EHCC patients was 2.39-fold higher than that in healthy controls ($P = 0.002$). The optimal cut-off value for HDGF was 122.15 pg/mL, providing a sensitivity of 66.27 % and a specificity of 88.24 %. The area under the curve (AUC) of HDGF was 0.807 (95 % confidence interval 0.730-0.870), demonstrating that HDGF was a potential biomarker for EHCC. CONCLUSIONS: HDGF was a valuable independent prognostic factor after curative resection in EHCC, and it provided an important basis for screening/treating high-risk patients. Meanwhile, our study indicated that serum HDGF levels can be used as a noninvasive and potential diagnostic marker for EHCC.

[531]

TÍTULO / TITLE: - The novel proteasome inhibitor carfilzomib induces cell cycle arrest, apoptosis and potentiates the anti-tumour activity of chemotherapy in rituximab-resistant lymphoma.

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

REVISTA / JOURNAL: - Br J Haematol. 2013 Jul 4. doi: 10.1111/bjh.12452.

●● Enlace al texto completo (gratis o de pago) [1111/bjh.12452](#)

AUTORES / AUTHORS: - Gu JJ; Hernandez-Ilizaliturri FJ; Kaufman GP; Czuczman NM; Mavis C; Skitzki JJ; Czuczman MS

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA.

RESUMEN / SUMMARY: - Targeting the proteasome system with bortezomib (BTZ) results in anti-tumour activity and potentiates the effects of chemotherapy/biological agents in multiple myeloma and B-cell lymphoma. Carfilzomib (CFZ) is a more selective proteasome inhibitor that is structurally distinct from BTZ. In an attempt to characterize its biological activity, we evaluated CFZ in several lymphoma pre-clinical models. Rituximab-sensitive cell lines (RSCL), rituximab-resistant cell lines (RRCL), and primary tumour cells derived from B-cell lymphoma patients were exposed to CFZ or BTZ. Cell viability and changes in cell cycle were determined. Western blots were performed to detect PARP-cleavage and/or changes in Bcl-2 (BCL2) family members. CFZ was 10 times more active than BTZ and exhibited dose- and time-dependent cytotoxicity. CFZ exposure induced apoptosis by upregulation of Bak (BAK1) and subsequent PARP cleavage in RSCL and RRCL; it was also partially caspase-dependent. CFZ induced G2/M phase cell cycle arrest in

RSCL. CFZ demonstrated the ability to overcome resistance to chemotherapy in RRCL and potentiated the anti-tumour activity of chemotherapy agents. Our data suggest that CFZ is able to overcome resistance to chemotherapeutic agents, upregulate pro-apoptotic proteins to promote apoptosis, and induce G2/M cell cycle arrest in lymphoma cells. Our pre-clinical data supports future clinical evaluation of CFZ in B-cell lymphoma.

[532]

TÍTULO / TITLE: - Erratum to: Differential toxicity biomarkers for irinotecan- and oxaliplatin- containing chemotherapy in colorectal cancer.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug;72(2):491. doi: 10.1007/s00280-013-2215-9.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2215-9](#)

AUTORES / AUTHORS: - Cortejoso L; Garcia MI; Garcia-Alfonso P; Gonzalez-Haba E; Escolar F; Sanjurjo M; Lomicronpez-Fernandez LA

INSTITUCIÓN / INSTITUTION: - Servicio de Farmacia, Hospital General Universitario Gregorio Marañón, Instituto de Investigaciones Sanitarias Gregorio Marañón, Doctor Esquerdo 46, 28007, Madrid, España.

[533]

TÍTULO / TITLE: - Melanoma genotypes and phenotypes get personal.

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

REVISTA / JOURNAL: - Lab Invest. 2013 Aug;93(8):858-67. doi: 10.1038/labinvest.2013.84. Epub 2013 Jul 1.

●● Enlace al texto completo (gratis o de pago) [1038/labinvest.2013.84](#)

AUTORES / AUTHORS: - Pimiento JM; Larkin EM; Smalley KS; Wiersma GL; Monks NR; Fedorenko IV; Peterson CA; Nickoloff BJ

INSTITUCIÓN / INSTITUTION: - [1] Division of Surgical Oncology, Lacks Cancer Center at Mercy Health-Saint Mary's, CHE/Trinity Health, Inc, Grand Rapids, MI, USA [2] Center for Translational Medicine, Van Andel Institute, Grand Rapids, MI, USA [3] College of Human Medicine, Michigan State University, Grand Rapids, MI, USA.

RESUMEN / SUMMARY: - Traditionally, the diagnosis of metastatic melanoma was terminal to most patients. However, the advancements towards understanding the fundamental etiology, pathophysiology, and treatment have raised melanoma to the forefront of contemporary medicine. Indeed, the evidence of durable remissions are being heard ever more frequently in clinics around the globe. Despite having more gene mutations per cell than any other type of cancer, investigators are overcoming complex genomic landscapes, signaling

pathways, and immune checkpoints by generating novel technological methods and clinical protocols with breath-taking speed. Significant progress in deciphering molecular genetics, epigenetics, kinase-driven networks, metabolomics, and immune-enhancing pathways to achieve personalized and positive outcomes has truly provided new hope for melanoma patients. However, obstacles requiring breakthroughs include understanding the influence of sunlight exposure on melanoma etiology, and overcoming all too frequently acquired drug resistance, complicating targeted therapy. Pathologists continue to have critically important roles in advancing the field, particularly in the area of transitioning from microscope-based diagnostic reports to pharmacogenomics through molecularly informed tumor boards. Although melanoma is no longer considered just 'one disease', pathologists will continue this rapidly progressing and exciting journey to identify tumor subtypes, to utilize tumorgraft or so-called patient-derived xenograft (PDX) models, and to develop companion diagnostics to keep pace with the bewildering breakthroughs occurring on a regular basis. Exactly which combination of drugs will ultimately be required to eradicate melanoma cells remains to be determined. However, it is clear that pathologists who are as dedicated to melanoma as the pioneering pathologist Dr Sidney Farber was committed to childhood cancers, will be required as the battle against melanoma continues. In this review, we describe what sets melanoma apart from other tumors, and demonstrate how lessons learned in the melanoma clinic are being transferred to many other types of aggressive neoplasms.

[534]

TÍTULO / TITLE: - Prognostic molecular markers in cancer - quo vadis?

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

REVISTA / JOURNAL: - Histopathology. 2013 May 7. doi: 10.1111/his.12184.

●● Enlace al texto completo (gratis o de pago) [1111/his.12184](#)

AUTORES / AUTHORS: - Soland TM; Brusevold IJ

INSTITUCIÓN / INSTITUTION: - Department of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo.

RESUMEN / SUMMARY: - Despite the tremendous number of studies of prognostic molecular markers in cancer, only a few such markers have entered clinical practise. The lack of clinical prognostic markers clearly reflects limitations in or an inappropriate approach to prognostic studies. This situation should be of great concern for the research community, clinicians and patients. In the present review, we evaluate immunohistochemical prognostic marker studies in oral squamous cell carcinomas (OSCC) from 2006 to 2012. We comment upon general issues such as study design, assay methods and statistical methods, applicable to prognostic marker studies irrespective of cancer type. The three most frequently studied markers in OSCC are reviewed. Our analysis revealed that most new molecular markers are reported only

once. To draw conclusions of clinical relevance based on the few markers that appeared in more than one study was problematic due to between-study heterogeneity. Currently, much valuable tissue material, time and money are wasted on irrelevant studies.

[535]

TÍTULO / TITLE: - Cytostatic and apoptotic effects of DNMT and HDAC inhibitors in endometrial cancer cells.

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

REVISTA / JOURNAL: - Curr Pharm Des. 2013 Jul 19.

AUTORES / AUTHORS: - Xu S; Ren J; Wang J; Liu Q; Zhang R; Jiang SW; Li J

INSTITUCIÓN / INSTITUTION: - Second Affiliated Hospital of Xi'an Jiaotong University Xi'an, Shanxi Province, China,710004.Jiang_s@mercuer.edu.

RESUMEN / SUMMARY: - DNA methyltransferase (DNMT) and histone deacetylase are key enzymes mediating the epigenetic regulation of gene expression. DNA hypermethylation and/or histone deacetylation in promoter regions is associated with downregulation or silencing of transcription. Epigenetic silencing of tumor suppressor genes plays an important role in malignant transformation. DNMT and HDAC inhibitors induce DNA demethylation and histone acetylation, respectively, leading to reactivation of silenced genes, and dramatic morphological and functional changes in cancer cells. In this study, we have conducted a series of experiments to characterize the effects of epigenetic inhibitors in endometrial cancer cells. Using cell lines representing different stages of endometrioid cancers, we examined the impact of DNMT inhibitor, ADC, and HDAC inhibitor, TSA, on cell cycle and apoptosis. We found that while both reagents were capable of inhibiting cell proliferation and inducing cell apoptosis, TSA appeared to be a more potent apoptosis inducer, but with a smaller effect on cell cycle. On the other hand, ADC exhibited strong effects on cell cycle regulation, but had smaller impact on cell apoptosis. We subsequently confirmed the presence of a strong synergism between DNMT and HDAC inhibitors. Thus, ADC and TSA exhibited strong cytostatic and apoptotic effects in endometrial cancer cell lines and the combined application may deliver the highest response in the clinical setting.

[536]

TÍTULO / TITLE: - Anti-miRNA-23^a Oligonucleotide Suppresses Glioma Cells Growth by Targeting Apoptotic Protease Activating Factor-1.

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

REVISTA / JOURNAL: - Curr Pharm Des. 2013 Jul 16.

AUTORES / AUTHORS: - Lian S; Shi R; Bai T; Liu Y; Miao W; Wang H; Liu X; Fan Y

INSTITUCIÓN / INSTITUTION: - Department of Surgery, The First Hospital of Shanxi Medical University, Taiyuan 030001, PR China.

fym13834155678@163.com.

RESUMEN / SUMMARY: - Background: Abnormal expression of microRNAs (miRNAs) is closely related to glioma, which is one of the most common malignant brain tumors. The current study is to identify the key miRNAs involved in the pathogenesis of glioma and to discover novel therapeutic targets for this disease. Materials and Methods: Total RNA was extracted from glioma tissues of 100 patients. The microRNA microarray and the northern blot were used to detect the changes of miRNAs expression in 7 pairs of glioma specimens. Relative expressions of miR-23^a were validated by real-time reverse transcription polymerase chain reaction (RT-PCR) with specific Taqman probes. In order to evaluate the role of miR-23^a, the miR-23^a mimics and anti-miR-23^a oligonucleotides were transfected to glioma cell lines; the cell proliferation, apoptosis, cell cycle percentage, cell migration and invasion abilities were evaluated in vitro. The target genes of miR-23^a were also investigated using the bioinformatics tools. The expression of the apoptotic protease activating factor-1 (APAF1), which might be one of the direct targets of miR-23^a, was also analyzed using the luciferase reporter assay and western blot analysis in 293T cells and glioma cell line, respectively. Results: The microRNA microarray and the northern blot results showed that the expressions of miR-23^a in glioma tissues were significantly upregulated. The miR-23^a expression levels identified using real time RT-PCR in tumor tissues of 79 samples were higher than in the matched adjacent tissues. By transfection of anti-miR-23^a oligonucleotide, the results showed that the proliferation, migration, and invasion of glioma cell lines were significantly suppressed. The bioinformatics searching results showed that APAF1 might be a direct target gene of miR-23^a, and it was supported by the luciferase reporter gene assay and western blot analysis results. Finally, experiments showed that overexpression of APAF1 suppressed glioma cell growth and promoted cell apoptosis. Conclusions: Our findings characterized the expression properties of miR-23^a, contributed to the function and molecular mechanism of miR-23^a in glioma and implied that miR-23^a might be employed as novel prognostic markers and therapeutic targets of glioma.

[537]

TÍTULO / TITLE: - ATG7 deficiency promote apoptotic death induced by Cisplatin in human esophageal squamous cell carcinoma cells.

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

REVISTA / JOURNAL: - Bull Cancer. 2013 Aug 1;100(7-8):15-21. doi: 10.1684/bdc.2013.1749.

●● Enlace al texto completo (gratis o de pago) [1684/bdc.2013.1749](#)

AUTORES / AUTHORS: - Zhu L; Du H; Shi M; Chen Z; Hang J

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197, Ruijin Er Road, 200025 Shanghai, China.

RESUMEN / SUMMARY: - Cisplatin-(DDP)-based adjuvant chemotherapy is widely used for the treatment of esophageal cancer. However, DDP-based combinatorial treatments can eventually result in tumor resistance response. Therefore, new therapeutic strategies and/or new adjuvant drugs still need to be explored. In this study, we aimed to understand the role of autophagy in ESCC cells resistance to Cisplatin and discuss its potential therapeutic implication. We found that exposure to Cisplatin induced a significant increase in LC3 formation. While the proliferation of ESCC cells was inhibited upon Cisplatin exposure, inhibition of autophagy by ATG7 interference further increased the sensitivity to chemotherapy. Meanwhile, the Cisplatin-induced apoptotic cell death was significantly enhanced. These results suggest that autophagy may function importantly in ESCC cells resistance to Cisplatin. Intriguingly, the resistance could be recovered by autophagy inhibition. This also points to potential therapy for ESCC by perturbing autophagy.

[538]

TÍTULO / TITLE: - Sensitivity to epidermal growth factor receptor tyrosine kinase inhibitor requires E-cadherin in esophageal cancer and malignant pleural mesothelioma.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2401-8.

AUTORES / AUTHORS: - Xin HW; Yang JH; Nguyen DM

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

RESUMEN / SUMMARY: - BACKGROUND/AIM: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has limited anticancer efficacy in EGFR-positive esophageal cancer (EsC) and malignant mesothelioma (MPM). The underlying molecular mechanism of resistance to EGFR-TKI in these types of cancer remains unclear. MATERIALS AND METHODS: We tested sensitivity to EGFR-TKI, expression/activity of common signal transduction pathways and epithelial to mesenchymal transition (EMT) gene signatures in 14 EsC and MPM cultured cell lines in vitro. RESULTS: More than 50% EGFR-positive EsC and MPM cells were resistant to EGFR-TKI, and susceptibility to EGFR-TKI growth-inhibitory effect correlated positively with expression of E-cadherin (epithelial gene marker) and negatively with mesenchymal gene markers. Acquired resistance to EGFR-TKI in intrinsically sensitive cancer cells coincided with spontaneous loss of E-cadherin, while ectopic expression of E-cadherin sensitized resistant cells to EGFR-TKI. CONCLUSION: E-Cadherin expression appears to be not only a strong biomarker but also a functional requirement and potential therapeutic target for sensitivity to EGFR-TKI.

[539]

TÍTULO / TITLE: - Erlotinib-induced autophagy in epidermal growth factor receptor mutated non-small cell lung cancer.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Jun 12. pii: S0169-5002(13)00224-9. doi: 10.1016/j.lungcan.2013.05.012.

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

[1016/j.lungcan.2013.05.012](#)

AUTORES / AUTHORS: - Li YY; Lam SK; Mak JC; Zheng CY; Ho JC

INSTITUCIÓN / INSTITUTION: - Division of Respiratory Medicine, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region.

RESUMEN / SUMMARY: - **PURPOSE:** Erlotinib is a commonly used tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC). Autophagy is a catabolic process in response to stress and deprivation of nutrients. This study aims to investigate whether autophagy confers acquired resistance to erlotinib treatment in NSCLC. **METHODS:** Four NSCLC cell lines (HCC827, HCC4006, H358 and H1975) with different epidermal growth factor receptor (EGFR) mutation status (exon 19 deletion, exon 19 deletion, wild-type and L858R/T790M respectively) were selected. MTT assay, crystal violet staining and Annexin-V assay were performed to determine cell viability and apoptosis. Autophagic proteins were detected by Western blot. Acidic vesicular organelle (AVO) formation was determined by acridine orange staining. Autophagy inhibitor (chloroquine) and RNA interference were used to demonstrate the biological effect of erlotinib-induced autophagy. **RESULTS:** In line with EGFR mutation status, it was shown that both HCC827 and HCC4006 cells were sensitive to erlotinib, while H358 and H1975 cell lines were resistant. Erlotinib treatment at clinically relevant concentrations induced autophagy (increased LC3II expression, Atg-5/Atg12 conjugation, formation of AVO and p62 degradation) in sensitive NSCLC cell lines, via p53 nuclear translocation, AMPK activation and mTOR suppression. Addition of chloroquine, as an autophagy inhibitor, enhanced erlotinib sensitivity in sensitive cells. Similarly, silencing of Atg5 or Beclin-1 significantly increased sensitivity to erlotinib in both sensitive cell lines. In contrast, there was no induction of autophagy in resistant H358 and H1975 cell lines upon erlotinib exposure. **CONCLUSIONS:** Erlotinib can induce both apoptosis and autophagy in sensitive NSCLC cell lines with activating EGFR mutation (exon 19 del). Inhibition of autophagy can further enhance sensitivity to erlotinib in EGFR-mutated NSCLC, suggesting that autophagy may serve as a protective mechanism.

[540]

TÍTULO / TITLE: - Lclet 4 enhances pro-apoptotic and anti-invasive effects of mitoxantrone on human prostate cancer cells - in vitro study.

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

REVISTA / JOURNAL: - Acta Biochim Pol. 2013 Jul 18.

AUTORES / AUTHORS: - Koczurkiewicz P; Podolak I; Wojcik KA; Galanty A; Madeja Z; Michalik M; Czyz J

INSTITUCIÓN / INSTITUTION: - Department of Cell Biology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland and Department of Pharmacognosy, Faculty of Pharmacy, Medical College, Jagiellonian University, Krakow, Poland.

RESUMEN / SUMMARY: - Triterpene saponosides are widely distributed plant secondary metabolites characterized by relatively low systemic cytotoxicity and a range of biological activities. These include anti-inflammatory, antimicrobial, vasoprotective and antitumor properties. In particular, the ability of saponins to enhance the cytotoxicity of chemotherapeutic drugs opened perspectives for their application in combined cancer chemotherapy. Here, we used human prostate cancer DU-145 cells as an in vitro model to elucidate the synergy of the interactions between biological activities of an oleanane type 13beta,28-epoxy triterpene saponoside (Lclet 4) and mitoxantrone, which is a cytostatic drug commonly used in prostate cancer therapy. No cytotoxic or pro-apoptotic effect of Lclet 4 and mitoxantrone administered at the concentrations between 0.05 and 0.1 microg/ml could be seen. In contrast, cocktails of these agents exerted synergistic pro-apoptotic effects, accompanied by the activation of the caspase 3/7 system. This effect was paralleled by attenuating effects of Lclet 4/mitoxantrone cocktails on the invasive potential, metalloproteinase expression and motility of DU-145 cells. Multifaceted and additive effects of Lclet 4 and mitoxantrone on basic cellular traits crucial for prostate cancer progression indicate that the combined application of both agents at systemically neutral concentrations may provide the basis for new promising strategies of prostate cancer chemotherapy.

[541]

TÍTULO / TITLE: - Tumour antigen targeted monoclonal antibodies incorporating a novel multimerisation domain significantly enhance antibody dependent cellular cytotoxicity against colon cancer.

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

REVISTA / JOURNAL: - Eur J Cancer. 2013 Jul 18. pii: S0959-8049(13)00484-X. doi: 10.1016/j.ejca.2013.06.009.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejca.2013.06.009

AUTORES / AUTHORS: - Jain A; Poonia B; So EC; Vyzasatya R; Burch EE; Olsen HS; Merigeon EY; Block DS; Zhang X; Schulze DH; Hanna NN; Twadell WS; Yfantis HG; Chan SL; Cai L; Strome SE

INSTITUCIÓN / INSTITUTION: - Baltimore Veterans Administration Medical Center, Section of Surgical Oncology, and Research and Development Service, 10 N. Greene Street, 5C Surgical Services Area, Baltimore, MD 21201, USA; Division of General and Oncologic Surgery, University of Maryland School of Medicine, 22 S. Greene Street, Room S4B12, Baltimore, MD 21201, USA; Department of Otorhinolaryngology-Head and Neck Surgery, University of Maryland School of Medicine, 16 S. Eutaw Street, Baltimore, MD 21201, USA. Electronic address: ajain@smail.umaryland.edu.

RESUMEN / SUMMARY: - Tumour antigen targeted antibodies (mAbs) can induce natural killer (NK) cells to kill tumours through antibody dependent cellular cytotoxicity (ADCC) upon engagement of NK cell expressed FcγRIIIa. FcγRIIIa polymorphisms partially dictate the potency of the ADCC response. The high affinity FcγRIIIa-158-valine (V) polymorphism is associated with more potent ADCC response than the low affinity FcγRIIIa-158-phenylalanine (F) polymorphism. Because approximately 45% of patients are homozygous for the FcγRIIIa-158-F polymorphism (FF genotype), their ability to mount ADCC is impaired. We investigated whether a novel mAb capable of binding multiple antigen specific targets and engaging multiple low affinity FcγRIIIa receptors could further enhance ADCC against colon cancer in vitro. Specifically, we generated a novel anti-epidermal growth factor receptor (EGFR) antibody (termed a stradobody) consisting of an unmodified Fab sequence and two Immunoglobulin G, subclass 1 (IgG1) Fc domains separated by an isoleucine zipper domain and the 12 amino-acid IgG2 hinge. The stradobody framework induced multimerisation and was associated with increased binding to the EGFR and FcγRIIIa. From a functional perspective, when compared to an unmodified anti-EGFR mAb with a sequence identical to cetuximab (a commercially available anti-EGFR mAb), stradobodies significantly enhanced ADCC. These effects were observed using both KRAS wild type HT29 and KRAS mutant SW480 colon cancer cells as targets, and by NK cells obtained from healthy donors and a cohort of patients with colon cancer. These data suggest that high avidity cross-linking of multiple tumour surface antigens and multiple NK cell associated FcγRIIIa molecules can enhance ADCC and partially overcome impaired ADCC by FF genotype individuals in vitro.

[542]

TÍTULO / TITLE: - A novel hydroxysuberamide derivative potentiates MG132-mediated anticancer activity against human hormone refractory prostate cancers-the role of histone deacetylase and endoplasmic reticulum stress.

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

REVISTA / JOURNAL: - Prostate. 2013 Sep;73(12):1270-80. doi: 10.1002/pros.22641. Epub 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1002/pros.22641](https://doi.org/10.1002/pros.22641)

AUTORES / AUTHORS: - Chen YC; Huang WJ; Hsu JL; Yu CC; Wang WT; Guh JH

INSTITUCIÓN / INSTITUTION: - College of Medicine, School of Pharmacy, National Taiwan University, Taipei, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND: Histone deacetylase (HDAC) inhibitors are successful for treatment of advanced cutaneous T-cell lymphoma but only show modest effect in solid tumors. Approaches for HDAC inhibitors to improve activity against solid tumors are necessary. METHODS: Sulforhodamine B assay and flow cytometric analysis detected cell proliferation and cell-cycle progression, respectively. Protein expression was determined by Western blotting. Comet assay and DNA end-binding activity of Ku proteins detected DNA damage and DNA repair activity, respectively. siRNA technique was used for knockdown of specific cellular target. RESULTS: WJ25591 displayed inhibitory activity against HDAC1 and cell proliferation in human hormone-refractory prostate cancers PC-3 and DU-145. WJ25591 caused an arrest of cell-cycle at both G1- and G2-phase and increased protein expressions of p21 and cyclin E, followed by cell apoptosis. WJ25591-induced Bcl-2 down-regulation and activation of caspase-9, -8, and -3, suggesting apoptotic execution through both intrinsic and extrinsic apoptotic pathways. WJ25591 also significantly inhibited DNA repair activity but not directly induced DNA damage. Moreover, the proteasome inhibitor MG-132 dramatically sensitized WJ25591-induced cell apoptosis. The siRNA technique demonstrated that endoplasmic reticulum (ER) stress, in particular CHOP/GADD153 up-regulation, contributed to the synergistic effect. CONCLUSIONS: The data suggest that WJ25591 inhibited HDAC activity, leading to cell-cycle arrest and inhibition of DNA repair. Caspase cascades are subsequently triggered to execute cell apoptosis. MG-132 dramatically sensitizes WJ25591-mediated apoptosis, at least partly, through ER stress response. The data also reveal that combination of HDAC inhibitors and proteasome inhibitors may be a potential strategy against hormone-refractory prostate cancers. Prostate 73: 1270-1280, 2013. © 2013 Wiley Periodicals, Inc.

[543]

TÍTULO / TITLE: - Cellular Impedance Assays for Predictive Preclinical Drug Screening of Kinase Inhibitor Cardiovascular Toxicity.

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

REVISTA / JOURNAL: - Toxicol Sci. 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1093/toxsci/kft167](#)

AUTORES / AUTHORS: - Lamore SD; Kamendi HW; Scott CW; Dragan YP; Peters MF

INSTITUCIÓN / INSTITUTION: - Molecular Toxicology, Global Safety Assessment, AstraZeneca Pharmaceuticals, Waltham, MA, USA 02451.

RESUMEN / SUMMARY: - Cardiovascular (CV) toxicity is a leading contributor to drug attrition. Implementing earlier testing has successfully reduced hERG-related arrhythmias. However, analogous assays targeting functional CV effects remain elusive. Demand to address this gap is particularly acute for kinase inhibitors (KI) which suffer frequent CV toxicity. The drug class also presents some particularly challenging requirements for assessing functional CV toxicity. Specifically, an assay must sense a downstream response that integrates diverse kinase signaling pathways. In addition, sufficient throughput is essential for handling inherent KI nonselectivity. A new opportunity has emerged with cellular impedance technology which detects spontaneous beating cardiomyocytes. Impedance assays sense morphology changes downstream of cardiomyocyte contraction. To evaluate cardiomyocyte impedance assays for KI screening, we investigated two distinct KI classes where CV toxicity was discovered late and target risks remain unresolved. Microtubule-associated protein/microtubule affinity-regulating kinase (MARK) inhibitors decrease blood pressure in dogs while checkpoint kinase (Chk) inhibitors (AZD7762, SCH900776) exhibit dose-limiting CV toxicities in clinical trials. These in vivo effects manifested in vitro as cardiomyocyte beat cessation. MARK effects were deemed mechanism-associated since beat inhibition potencies correlated with kinase inhibition, and gene knockdown and microtubule-targeting agents suppressed beating. MARK inhibitor impedance and kinase potencies aligned with rat blood pressure effects. Chk inhibitor effects were judged off-target since Chk and beat inhibition potencies did not correlate and knockdowns did not alter beating. Taken together, the data demonstrate that cardiomyocyte impedance assays can address three unmet needs- detecting KI functional cardiotoxicity in vitro, determining mechanism of action, and supporting safety structure-activity relationships.

[544]

TÍTULO / TITLE: - UDP-glucuronosyltransferase (UGT) 1^{a1}*28 Polymorphism-directed Phase II Study of Irinotecan with 5'-deoxy-5-fluorouridine (5'-DFUR) for Metastatic Colorectal Cancer.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):3423-30.

AUTORES / AUTHORS: - Kanekiyo S; Hazama S; Kondo H; Nagashima A; Eto R; Yoshida S; Shimizu R; Araki A; Yamamoto T; Uchiyama T; Yoshino S; Okayama N; Hinoda Y; Oka M

INSTITUCIÓN / INSTITUTION: - Professor and Chairman, Department of Digestive Surgery and Surgical Oncology (Surgery II), Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi 755-8505, Japan. 2geka-1@yamaguchi-u.ac.jp.

RESUMEN / SUMMARY: - Aim: We performed a phase II study of irinotecan with 5'-deoxy-5-fluorouridine (5'-DFUR) for metastatic colorectal cancer based on

UDP-glucuronosyltransferase (UGT) 1^{a1} polymorphism. PATIENTS AND METHODS: A total of 28 patients were enrolled. The dose of irinotecan was 150 mg/m² for patients with the *1/*1 wild-type genotype, and 70 mg/m² for those with the *1/*28 mutated genotype. The primary end-point was the response rate (RR); secondary end-points were safety, time to treatment failure (TTF), and overall survival (OS). RESULTS: In 28 patients total, genotype was wild-type in 22 and mutated in six. The RR was *1/*1 (22.7%; wild-type) vs. *1/*28 (16.7%; mutated); the median TTF was 5 months vs. 4.5 months, and the median OS was 13 months vs. 17.5 months, respectively. None of these differences were significant. Toxicities of grade 3 or higher were neutropenia (9.0% vs. 0%, respectively) and diarrhea (13.6% vs. 0%, respectively). CONCLUSION: This genotype-oriented therapy was effective and safe, and thus appears useful for patients who have complications or advanced age.

[545]

TÍTULO / TITLE: - CD146 Protein as a Marker to Predict Postoperative Liver Metastasis in Colorectal Cancer.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 Jul-Aug;28(6):466-70. doi: 10.1089/cbr.2012.1426. Epub 2013 Jun 8.

●● Enlace al texto completo (gratis o de pago) [1089/cbr.2012.1426](#)

AUTORES / AUTHORS: - Tian B; Zhang Y; Li N

INSTITUCIÓN / INSTITUTION: - 1 Department of Neurology, First Affiliated Hospital of Liaoning Medical College, Jinzhou, China .

RESUMEN / SUMMARY: - Abstract Objective: To study the expression and regulatory effects of CD146 protein in colorectal cancer and the correlation between CD146 protein expression and the prognosis of colorectal cancer. Materials and Methods: The CD146 protein level was detected by immunohistochemistry staining. The relationship between CD146 expression and clinicopathological parameters of colorectal cancer was determined. Results: It was observed that 216 (20.00%) of the 1080 cases positively expressed CD146 protein. Univariate analyses indicated that CD146 expression was related to histological grade, Duke's stage, and liver metastasis (p=0.001, 0.001, and 0.001, respectively). Spearman correlation analysis showed that CD146 expression has line correlation to histological grade, Duke's stage, and liver metastasis (p=0.02, 0.01 and 0.001, respectively). After multivariate analysis, Duke's stage and CD146 were related to liver metastasis (p=0.01 and 0.001, respectively). In the Cox regression test, histological grade, Duke's stage, and CD146 were detected as the independent prognostic factors (p=0.045, 0.01, and 0.001, respectively). Conclusions: CD146 protein may be a potential biomarker for the postoperative liver metastasis of colorectal cancer.

[546]

TÍTULO / TITLE: - Prognostic Significance of beta-Human Chorionic Gonadotropin and PAX8 Expression in Anaplastic Thyroid Carcinoma.

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

REVISTA / JOURNAL: - Thyroid. 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1089/thy.2013.0117](#)

AUTORES / AUTHORS: - Becker N; Chernock RD; Nussenbaum B; Lewis Jr JS

INSTITUCIÓN / INSTITUTION: - Washington University in St. Louis, Pathology and Immunology, Saint Louis, Missouri, United States ; nbecker@path.wustl.edu.

RESUMEN / SUMMARY: - Background: Anaplastic thyroid carcinoma (ATC) is a rare, aggressive malignancy with a median survival of five months.

Multimodality treatment is associated with some improvement in survival, but patients are only infrequently curable. Although beta-hCG secretion has been reported in many neoplasms, it has never been described in ATC. The objectives of this study were to report a case of beta-hCG secreting ATC and to study the expression and significance of beta-hCG and PAX8 in an institutional cohort of ATC. Methods: The sentinel case was characterized and then immunohistochemistry was performed for beta-hCG and PAX8 on 30 ATC patients. Clinical follow up was obtained by chart review. Results: The sentinel patient with beta-hCG positive ATC had a dramatic response to chemotherapy and radiation. After surgical excision of residual disease, the patient developed a regional recurrence of differentiated thyroid carcinoma at 18 months. However, she is now 30 months post initial therapy with no evidence of disease and no detectable serum beta-hCG or thyroglobulin. Five of the 30 (17%) total ATC were positive for beta-hCG and 18 (60%) for PAX8. Outcomes for the beta-hCG positive cases were not significantly different than for negative ones. However, none of the other four beta-hCG positive ATC patients received treatment with chemoradiation. Interestingly, PAX8 positivity correlated with statistically significantly better overall survival ($p = 0.016$). Conclusions: Although only a single case, our findings suggest that beta-hCG positive ATC may be a subtype of ATC, or possibly even a unique entity, which responds to aggressive medical treatment and has a more favorable outcome.

[547]

TÍTULO / TITLE: - The deactivation of signal transducer and activator of transcription-3 activation signaling by emodin inhibits growth and induces apoptosis in orthotopic hepatocellular carcinoma model.

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

REVISTA / JOURNAL: - Br J Pharmacol. 2013 Jul 15. doi: 10.1111/bph.12302.

●● Enlace al texto completo (gratis o de pago) [1111/bph.12302](#)

AUTORES / AUTHORS: - Subramaniam A; Shanmugam MK; Ong TH; Li F; Perumal E; Chen L; Vali S; Abbasi T; Kapoor S; Ahn KS; Kumar AP; Hui KM; Sethi G

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597; Molecular Toxicology Lab, Department of Biotechnology, Bharathiar University, Coimbatore 641046, Tamilnadu, India.

RESUMEN / SUMMARY: - **BACKGROUND AND PURPOSE:** Aberrant activation of signal transducer and activators of transcription 3 (STAT3) is frequently encountered and promotes proliferation, survival, metastasis and angiogenesis in hepatocellular carcinoma (HCC). In the present study, we investigated whether emodin mediates its effect through interference with the STAT3 activation pathway in HCC. **EXPERIMENTAL APPROACH:** The effect of emodin on STAT3 activation, associated protein kinases, and apoptosis was investigated using various HCC cell lines. Additionally we also explicitly tested if emodin effects were mediated by STAT3 inhibition using a predictive tumor technology. The in vivo effect of emodin on the orthotopic mouse model was also examined. **KEY RESULTS:** We found that emodin suppressed STAT3 activation in a dose- and time-dependent manner in HCC cells. The suppression was mediated through the modulation of activation of upstream kinases c-Src, Janus-activated kinase 1, and Janus-activated kinase 2. Vanadate treatment reversed emodin-induced down-regulation of STAT3, suggesting the involvement of a tyrosine phosphatase. Indeed, we found that emodin induced the expression of tyrosine phosphatase SHP-1 that correlated with the down-regulation of constitutive STAT3 activation. Interestingly, deletion of SHP-1 gene by siRNA abolished the ability of this quinone to inhibit STAT3 activation. Finally, when administered i.p., emodin inhibited the growth of human HCC orthotopic tumors in male athymic nu/nu mice and STAT3 activation in tumor tissues. **CONCLUSIONS AND IMPLICATIONS:** Overall, our results suggest that emodin is mediating its effects predominantly through inhibition of STAT3 signaling cascade and thus has an enormous potential for the treatment cancers harboring constitutively activated STAT3.

[548]

TÍTULO / TITLE: - The Radiosensitizing Effect of Paeonol on Lung Adenocarcinoma by Augmentation of Radiation-induced Apoptosis and Inhibition of the PI3K/Akt Pathway.

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

REVISTA / JOURNAL: - Int J Radiat Biol. 2013 Jul 23.

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

[3109/09553002.2013.825058](#)

AUTORES / AUTHORS: - Lei Y; Li HX; Jin WS; Peng WR; Zhang CJ; Bu LJ; Du YY; Ma T; Sun GP

RESUMEN / SUMMARY: - Abstract Purpose: To investigate the radiosensitizing effect and mechanism of action by the natural product-Paeonol on lung adenocarcinoma both in vitro and in vivo. Materials and methods: Two lung adenocarcinoma cell lines (human lung adenocarcinoma cell line A549 and mouse Lewis lung carcinoma (LLC) cell line) were chosen for this research. In order to select the experimental concentrations of Paeonol, cytotoxicity was determined using a MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. A clonogenic assay was performed to measure the radiosensitizing effects. Apoptosis was determined by the TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick and labeling) assay and flow cytometry. Protein expression was analyzed by Western blotting. To test the radiosensitizing effect in vivo, a transplanted tumor model was established. Results: The MTT assay showed that Paeonol inhibited proliferation of cells. Paeonol concentration ranged from an IC₅₀ (5% inhibiting concentration) to an IC₂₀ and was used at nontoxic concentrations for subsequent experiments. The clonogenic assay showed that Paeonol enhanced the radiosensitivity of cells. Data from the TUNEL assay and flow cytometry verified that Paeonol enhanced radiation-induced apoptosis. Paeonol inhibited the activation of the PI3K/AKT (Phosphatidylinositol 3-kinase/ Protein Kinase B) pathway and down-regulated the expression of COX-2 (Cyclooxygenase-2) and Survivin. Paeonol (1718mg/kg) combined with 10Gy irradiation inhibited the growth of a transplanted tumor model in vivo, resulting in the longest tumor growth time, tumor growth delay and the highest inhibition ratio when compared with the radiotherapy alone group. Conclusions: It is reported for the first time that Paeonol has a radiosensitizing effect on lung adenocarcinoma both in vitro and in vivo. This effect could be related to the augmentation of radiation-induced apoptosis and the inhibition of the PI3K/Akt signalling pathway and its downstream proteins: COX-2 and Survivin.

[549]

TÍTULO / TITLE: - Discovery of 7-azaindole based anaplastic lymphoma kinase (ALK) inhibitors: Wild type and mutant (L1196M) active compounds with unique binding mode.

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

REVISTA / JOURNAL: - Bioorg Med Chem Lett. 2013 Sep 1;23(17):4911-8. doi: 10.1016/j.bmcl.2013.06.071. Epub 2013 Jul 4.

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

[1016/j.bmcl.2013.06.071](#)

AUTORES / AUTHORS: - Gummadi VR; Rajagopalan S; Looi CY; Paydar M; Renukappa GA; Ainan BR; Krishnamurthy NR; Panigrahi SK; Mahasweta K; Raghuramachandran S; Rajappa M; Ramanathan A; Lakshminarasimhan A; Ramachandra M; Wong PF; Mustafa MR; Nanduri S; Hosahalli S

INSTITUCIÓN / INSTITUTION: - Aurigene Discovery Technologies Ltd., #39/40, KIADB Industrial Area, Hosur Road, Electronic City Phase-II, Bangalore 560100, India.

RESUMEN / SUMMARY: - We have identified a novel 7-azaindole series of anaplastic lymphoma kinase (ALK) inhibitors. Compounds 7b, 7m and 7n demonstrate excellent potencies in biochemical and cellular assays. X-ray crystal structure of one of the compounds (7k) revealed a unique binding mode with the benzyl group occupying the back pocket, explaining its potency towards ALK and selectivity over tested kinases particularly Aurora-A. This binding mode is in contrast to that of known ALK inhibitors such as Crizotinib and NVP-TAE684 which occupy the ribose binding pocket, close to DFG motif.

[550]

TÍTULO / TITLE: - Prognosis of Differentiated Thyroid Cancer in Relation to Serum TSH And Thyroglobulin Antibody Status at Time of Diagnosis.

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

REVISTA / JOURNAL: - Thyroid. 2013 Jun 3.

●● Enlace al texto completo (gratis o de pago) [1089/thy.2013.0062](#)

AUTORES / AUTHORS: - McLeod DS; Cooper DS; Ladenson PW; Ain KB; Brierley J; Fein HG; Haugen BR Md; Jonklaas J; Magner J; Ross DD; Young MS Md; Steward D; Maxon H; Sherman SI

INSTITUCIÓN / INSTITUTION: - Royal Brisbane & Women's Hospital, Department of Internal Medicine & Aged Care, Butterfield St, Herston, Queensland, Australia, 4029, +61 7 3646 8111 ; donald.mcleod@qimr.edu.au.

RESUMEN / SUMMARY: - Background: Serum thyrotropin (TSH) concentration and thyroid autoimmunity may be of prognostic importance in differentiated thyroid cancer (DTC). Preoperative serum TSH level has been associated with higher DTC stage in cross-sectional studies; data are contradictory on the significance of thyroid autoimmunity at the time of diagnosis. Objective: We sought to assess whether preoperative serum TSH and perioperative anti-thyroglobulin antibodies (TgAb) were associated with thyroid cancer stage and outcome in DTC patients followed by the National Thyroid Cancer Treatment Cooperative Study, a large multicenter thyroid cancer registry. Methods: Patients registered after 1996 with available preoperative serum TSH (n=617; the TSH cohort) or perioperative TgAb status (n=1770; the TgAb cohort) were analyzed for tumor stage, persistent disease, recurrence, and overall survival (OS) (median follow-up 5.5 years). Parametric tests assessed log transformed TSH, and categorical variables were tested with chi2. Disease-free survival (DFS) and OS was assessed with Cox models. Results: Geometric mean serum TSH levels were higher in patients with higher stage disease (stage III/IV=1.48 vs. 1.02 mU/L for stages I/II; P=0.006). The relationship persisted in those aged >=45 years after adjusting for gender (P=0.01). Gross extrathyroidal extension (P=0.03) and presence of cervical lymph node metastases (P=0.003) were also

significantly associated with higher serum TSH. Disease recurrence and all-cause mortality occurred in 37 and 38 TSH cohort patients respectively, which limited the power for survival analysis. Positive TgAb was associated with lower stage on univariate analysis (positive TgAb in 23.4% vs. 17.8% of stage I/II vs. III/IV patients, respectively; $P=0.01$), although the relationship lost significance when adjusting for age and gender ($P=0.34$). Perioperative TgAb was not an independent predictor of DFS (hazard ratio [HR]=1.12 [95%CI=0.74-1.69]) or OS (HR=0.98 [95%CI=0.56-1.72]). Conclusions: Preoperative serum TSH level is associated with higher DTC stage, gross extrathyroidal extension, and neck node metastases. Perioperative TgAb is not an independent predictor of DTC prognosis. A larger cohort is required to assess whether preoperative serum TSH level predicts recurrence or mortality.

[551]

TÍTULO / TITLE: - Circulating miR-22, miR-24 and miR-34^a as novel predictive biomarkers to pemetrexed-based chemotherapy in advanced non small cell lung cancer.

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

REVISTA / JOURNAL: - J Cell Physiol. 2013 Jun 24. doi: 10.1002/jcp.24422.

●● Enlace al texto completo (gratis o de pago) [1002/jcp.24422](#)

AUTORES / AUTHORS: - Franchina T; Amodeo V; Bronte G; Savio G; Ricciardi GR; Picciotto M; Russo A; Giordano A; Adamo V

INSTITUCIÓN / INSTITUTION: - Unit of Medical Oncology, A.O.O.R. Papardo-Piemonte & Department of Human Pathology, University of Messina, Italy.

RESUMEN / SUMMARY: - BACKGROUND: Pemetrexed has been widely used in patients with advanced non small cell lung cancer (NSCLC). The clinical relevance of polymorphisms of folate pathway genes for pemetrexed metabolism have not been fully elucidated yet. The aim of this study was to evaluate the expression levels of circulating miR-22, miR-24 and miR-34^a, possibly involved in folate pathway, in NSCLC patients treated with pemetrexed compared with healthy controls and to investigate their impact on patient clinical outcomes. METHODS: A total of 22 consecutive patients with advanced NSCLC, treated with pemetrexed-based chemotherapy and 27 age and sex matched healthy controls were included in this preliminary analysis. miR-22, miR-24 and miR-34^a targets were identified by TargetScan 6.2 algorithm, validating the involvement of these microRNAs in folate pathway. MicroRNAs were isolated from whole blood and extracted with miRNAeasy Mini Kit (Qiagen). miRNA profiling was performed using Real-Time PCR. SPSS 17 was used to data analysis. RESULTS: miR-22, miR-24 and miR-34^a were found upregulated ($p < 0.05$) in NSCLC patients versus healthy controls. Higher expression levels were recorded for miR-34^a. Nevertheless, significantly higher miR-22 expression was observed in patients developing progressive disease ($p = 0.03$). No significant associations with clinical outcome were recorded for miR-

24 and miR-34^a. CONCLUSIONS: Albeit preliminary, these data support the involvement of miR-22, miR-24 and miR-34^a in advanced NSCLC. The correlation between high expression of miR-22 in whole blood and the lack of response in pemetrexed treated NSCLC patients indicates that miR-22 could represent a novel predictive biomarker for pemetrexed-based treatment. J. Cell. Physiol. © 2013 Wiley Periodicals, Inc.

[552]

TÍTULO / TITLE: - COX-2 promotes breast cancer cell radioresistance via p38/MAPK-mediated cellular anti-apoptosis and invasiveness.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 15.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0840-](#)

[X](#)

AUTORES / AUTHORS: - Lin F; Luo J; Gao W; Wu J; Shao Z; Wang Z; Meng J; Ou Z; Yang G

INSTITUCIÓN / INSTITUTION: - Cancer Research Laboratory, Fudan University Shanghai Cancer Center, Shanghai, 200032, China.

RESUMEN / SUMMARY: - Radioresistance is one of the major barriers to improve the survival rate of breast cancer patients. Cyclooxygenase 2 (COX-2) is usually overexpressed in highly invasive and metastatic breast cancer, which may indicate an association with breast cancer radioresistance. The function role of COX-2 was investigated by using a radioresistant breast cancer cell line MDA-MB-231/RR10 and its parental cell line MDA-MB-231 cells before or after COX-2 was silenced by a specific small hairpin RNA (shRNA). The cell proliferation, migration, invasion, colony formation, and apoptosis were measured by CCK-8, scratch-wound, transwell, clone formation assay, and flow cytometry. Protein and mRNA expression were analyzed by Western blot and quantitative reverse transcriptase-polymerase chain reaction. COX-2 is upregulated in MDA-MB-231/RR10 cells compared with in MDA-MB-231 cells, and silencing of COX-2 expression by shRNA in MDA-MB-231/RR10 cells decreases the expression of Bcl-2 and Bcl-XL, but increases the proapoptotic protein BAK, leading to the increased apoptosis following treatment with gamma-irradiation in comparison with those in control cells. Silencing of COX-2 also increases the expression of beta-catenin and E-cadherin, two anti-invasion proteins, resulting in reduced cell migration and invasion tested by transwell chambers and wound-healing assays. Further study demonstrated that COX-2-induced radioresistance is negatively regulated through the phosphorylation of p38 at Tyr182, and that the phosphorylation of p38 induced by TNF-alpha reduces the expression of Bcl-2, BCL-XL, but increases beta-catenin and E-cadherin, leading to the decreased invasiveness of cells. Our data suggest that COX-2, p38, Bcl-2, Bcl-XL, beta-catenin, and E-cadherin may be considered as potential therapeutic targets against radioresistant breast cancer.

[553]

TÍTULO / TITLE: - Challenges and controversies in the diagnosis of malignant mesothelioma: Part 2. Malignant mesothelioma subtypes, pleural synovial sarcoma, molecular and prognostic aspects of mesothelioma, BAP1, aquaporin-1 and microRNA.

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

REVISTA / JOURNAL: - J Clin Pathol. 2013 Jul 6.

●● Enlace al texto completo (gratis o de pago) [1136/jclinpath-2013-201609](#)

AUTORES / AUTHORS: - Henderson DW; Reid G; Kao SC; van Zandwijk N; Klebe S

INSTITUCIÓN / INSTITUTION: - Department of Surgical Pathology, SA Pathology, Flinders Medical Centre, Adelaide, South Australia.

RESUMEN / SUMMARY: - Pleural malignant mesothelioma (MM) includes several unusual and even rare but distinctive histological subtypes, in addition to the usual subdivision into epithelioid, biphasic and sarcomatoid MM. Criteria for discrimination between fibrous pleuritis versus desmoplastic mesothelioma include evidence of neoplastic invasion for diagnosis of desmoplastic MM, but this histological assessment is complicated by the recently-described 'fake fat phenomenon' in cases of fibrous pleuritis. The distinction between biphasic and monophasic synovial sarcoma of the pleura versus biphasic and sarcomatoid MM can be problematical and is most cogently based upon molecular detection of the t(X;18) translocation, whereas a clear diagnosis of MM for a pleural tumour histologically resembling synovial sarcoma is favoured by a negative result for this translocation and, probably, microRNA evidence supportive of a diagnosis of MM. Aquaporin-1 (AQP1) is a molecule involved in the growth of MM cells, and yet is a factor reported to correlate with improved survival rates for MM with an epithelioid component, in comparison to AQP1-poor MM, as assessed from AQP1 expression by epithelioid MM cells only (apart from co-expression by stromal endothelial cells in addition to the tumour cells). Recent reports have also focused upon germline mutations in the BRCA1-associated protein 1 (BAP1), not only in cases of familial mesothelioma, but also BAP1 deletion in sporadic MM. Prognostic factors for MM include not only the histological subtypes, but other independent variables that include (among others), AQP1 expression by mesothelioma cells, the clinical status of the patient, the serum neutrophil:lymphocyte ratio and blood thrombocytosis.

[554]

TÍTULO / TITLE: - ALLN hinders HCT116 tumor growth through Bax-dependent apoptosis.

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

REVISTA / JOURNAL: - Biochem Biophys Res Commun. 2013 Jul 26;437(2):325-30. doi: 10.1016/j.bbrc.2013.06.088. Epub 2013 Jul 2.

●● Enlace al texto completo (gratis o de pago) 1016/j.bbrc.2013.06.088

AUTORES / AUTHORS: - Li SZ; Zhang HH; Zhang JN; Zhang ZY; Zhang XF; Zhang XD; Du RL

INSTITUCIÓN / INSTITUTION: - College of Life Sciences, Wuhan University, Wuhan, Hubei 430072, China.

RESUMEN / SUMMARY: - Continual high expression of cysteine proteases calpain I and II have been implicated in tumorigenicity; conversely, N-acetyl-leu-leuorleucinal (ALLN), which inhibits calpain I and II, should also influence tumor growth and carcinogenesis. To explore the role of ALLN against colon cancer and in promoting apoptosis, we used colon cancer HCT116 cell lines, p53 or Bax-deficient HCT116 cell lines. Cell viability and tumor growth decreased in a concentration-dependent manner when treated with 0-26µM ALLN. Treatment with ALLN induced apoptosis in HCT116 cell; however, flow cytometry showed that apoptosis significantly decreased in Bax-deficient HCT116 cell lines, but not in p53-deficient HCT116 cell lines. In addition, the ALLN-induced apoptosis response was through Bax translocation from cytosol to mitochondria. In this study we showed intraperitoneally injected ALLN to inhibit colon tumor formation in nude mice, and found ALLN to inhibit tumor growth in colon cancer cells, mainly through apoptosis that depends on translocation of Bax to a mitochondrial endogenous pathway; this implies a molecular mechanism for ALLN against human colon cancer. These results suggest that ALLN could become a novel agent for prevention of colon cancer.

[555]

TÍTULO / TITLE: - Genomic and molecular aberrations in malignant peripheral nerve sheath tumor and their roles in personalized target therapy.

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

REVISTA / JOURNAL: - Surg Oncol. 2013 Jul 2. pii: S0960-7404(13)00064-9. doi: 10.1016/j.suronc.2013.06.003.

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

1016/j.suronc.2013.06.003

AUTORES / AUTHORS: - Yang J; Du X

INSTITUCIÓN / INSTITUTION: - Departments of Bone and Soft Tissue Tumor, Tianjin Medical University Cancer Hospital and Institute, Tianjin 30060, China. Electronic address: jilongyang@yahoo.com.

RESUMEN / SUMMARY: - Malignant peripheral nerve sheath tumors (MPNSTs) are malignant tumors with a high rate of local recurrence and a significant tendency to metastasize. Its dismal outcome points to the urgent need to establish better therapeutic strategies for patients harboring MPNSTs. The investigations of genomic and molecular aberrations in MPNSTs which detect many chromosomal aberrations, pathway abnormalities, and specific molecular

aberrant events would supply multiple potential therapy targets and contribute to achievement of personalized medicine. The involved genes in the significant gains aberrations include BIRC5, CCNE2, DAB2, DDX15, EGFR, DAB2, MSH2, CDK6, HGF, ITGB4, KCNK12, LAMA3, LOXL2, MET, and PDGFRA. The involved genes in the significant deletion aberrations include CDH1, GLTSCR2, EGR1, CTSB, GATA3, SULT2A1, GLTSCR2, HMMR/RHAMM, LICAM2, MMP13, p16/INK4a, RASSF2, NM-23H1, and TP53. These genetic aberrations involve in several important signaling pathways such as TFF, EGFR, ARF, IGF1R signaling pathways. The genomic and molecular aberrations of EGFR, IGF1R, SOX9, EYA4, TOP2A, ETV4, and BIRC5 exhibit great promise as personalized therapeutic targets for MPNST patients.

[556]

TÍTULO / TITLE: - Low differentiated microvascular density and low expression of platelet-derived growth factor-BB (PDGF-BB) predict distant metastasis and poor prognosis in clear cell renal cell carcinoma.

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

REVISTA / JOURNAL: - BJU Int. 2013 Aug;112(4):E415-23. doi: 10.1111/bju.12191.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12191](#)

AUTORES / AUTHORS: - Qi L; Du J; Zhang Z; Diao L; Chen X; Yao X

INSTITUCIÓN / INSTITUTION: - Department of Genitourinary Oncology, Tianjin Medical University Cancer Institute and Hospital; The Key Laboratory of Tianjin Cancer Prevention and Treatment, Tianjin, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To examine the prognostic significance of the expression of platelet-derived growth factor-BB (PDGF-BB) and differentiated microvascular density (MVD) in patients with clear cell renal cell carcinoma (ccRCC). **PATIENTS AND METHODS:** We used the vascular marker cluster of differentiation 34 (CD34) to identify tumour blood vessels. The expression of PDGF-BB and CD34 was detected by immunohistochemistry (IHC) in tissue microarrays (TMAs) from 100 ccRCCs. Prognostic effects of individual parameters were calculated using Cox regression models and Harrell's concordance index (c-index). **RESULTS:** Higher grade and more advanced stage ccRCCs had significantly less PDGF-BB expression and differentiated MVD ($P < 0.05$). Higher PDGF-BB expression was an independent prognostic factor for longer survival, and moreover, the final model built by the addition of PDGF-BB expression improved the predictive accuracy for disease-free survival (c-index 0.707) compared with the clinicopathological-based model (c-index 0.695). PDGF-BB expression was positively associated with differentiated MVD assessed by Spearman correlation and factor analysis ($r = 0.634$, $P < 0.001$). **CONCLUSION:** PDGF-BB is as a novel and promising prognostic marker and antiangiogenic therapeutic target for the treatment of ccRCC.

[557]

TÍTULO / TITLE: - Impact of EGFR tyrosine kinase inhibitors versus chemotherapy on the development of leptomeningeal metastasis in never smokers with advanced adenocarcinoma of the lung.

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

REVISTA / JOURNAL: - J Neurooncol. 2013 Jul 6.

- [Enlace al texto completo \(gratis o de pago\) 1007/s11060-013-1199-](#)

[Y](#)

AUTORES / AUTHORS: - Lee Y; Han JY; Kim HT; Yun T; Lee GK; Kim HY; Lee JS

INSTITUCIÓN / INSTITUTION: - Center for Lung Cancer, National Cancer Center, Ilsanro 323, Ilsandong-gu, Goyang, Gyeonggi, 410-769, Republic of Korea.

RESUMEN / SUMMARY: - This study investigated whether epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) increase the development of leptomeningeal metastasis (LM) compared with standard chemotherapy in EGFR mutation-enriched non-small cell lung cancer. The incidence of LM was longitudinally assessed in never smokers with advanced adenocarcinoma of the lung enrolled in a phase III randomized controlled study that compared gefitinib with gemcitabine plus cisplatin (GP) as first-line therapy (The First-SIGNAL study). Among 203 patients who were enrolled at the National Cancer Center Hospital (Goyang, Republic of Korea), LM occurred in 32 (15.8 %) with a minimum follow-up time of 55.1 months. The 1-, 2-, and 3-year actuarial incidence rates of LM were 5.3, 10.6, and 24.6 %, respectively. During first-line treatment, LM occurred in 2 patients (2.0 %) treated with gefitinib and in 3 patients (3.2 %) treated with GP. There was no difference in the incidence of LM during first-line treatment between the two groups ($P = 0.934$). The incidence of LM was significantly increased during second-line EGFR-TKI treatment compared with first-line EGFR-TKI treatment ($P = 0.041$). During the disease course, the cumulative incidence of LM was not significantly different between the two treatment groups ($P = 0.514$). The median time to LM was 21.4 and 24.0 months in the gefitinib and GP groups, respectively ($P = 0.895$). Similar trends were observed in the subset analysis with 23 EGFR-mutant patients. In conclusion, LM predominantly occurred in the late phase of disease in this population. EGFR-TKIs did not affect the incidence or timing of LM development.

[558]

TÍTULO / TITLE: - Caffeic acid phenethyl ester synergistically enhances docetaxel and paclitaxel cytotoxicity in prostate cancer cells.

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

REVISTA / JOURNAL: - IUBMB Life. 2013 Aug;65(8):716-29. doi: 10.1002/iub.1188. Epub 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [1002/iub.1188](https://doi.org/10.1002/iub.1188)

AUTORES / AUTHORS: - Tolba MF; Esmat A; Al-Abd AM; Azab SS; Khalifa AE; Mosli HA; Abdel-Rahman SZ; Abdel-Naim AB

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt; Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, TX, USA.

RESUMEN / SUMMARY: - Evidence is growing for the beneficial role of selective estrogen receptor modulators (SERM) in prostate diseases. Caffeic acid phenethyl ester (CAPE) is a promising component of propolis that possesses SERM activity. This study aimed at investigating the modulatory impact of CAPE on docetaxel (DOC) and paclitaxel (PTX) cytotoxicity in prostate cancer cells and exploring the possible underlying mechanisms for this chemomodulation. CAPE significantly increased DOC and PTX potency in PC-3, DU-145 and LNCaP prostate cancer cells. Combination index calculations showed synergistic interaction of CAPE/DOC and CAPE/PTX cotreatments in all the tested cell lines. Subsequent mechanistic studies in PC-3 cells indicated that cyclin D1 and c-myc were significantly reduced in the combined treatment groups with concurrent increase in p27(kip) . DNA-ploidy analysis indicated a significant increase in the percentage of cells in pre-G1 in CAPE/DOC and CAPE/PTX cotreatments. Decreased Bcl-2/Bax ratio together with increased caspase-3 activity and protein abundance were observed in the same groups. Estrogen receptor-beta (ER-beta) and its downstream tumor suppressor forkhead box O1 levels were significantly elevated in CAPE and combination groups compared to DOC or PTX-alone. ER-alpha and insulin-like growth factor-1 receptor protein abundance were reduced in the same groups. CAPE significantly reduced AKT, ERK and ER-alpha (Ser-167) phosphorylation in PC-3 cells. CAPE-induced inhibition of AKT phosphorylation was more prominent (1.7-folds higher) in cells expressing ER-alpha such as PC-3 compared to LNCaP. In conclusion, CAPE enhances the antiproliferative and cytotoxic effects of DOC and PTX in prostate cancer cells. This can be, at least partly, attributed to CAPE augmentation of DOC and PTX proapoptotic effects in addition to CAPE-induced alterations in ER-alpha and ER-beta abundance. © 2013 IUBMB Life, 65(8):716-729, 2013.

[559]

TÍTULO / TITLE: - Discoidin domain receptor 1 is associated with poor prognosis of non-small cell lung cancer and promotes cell invasion via epithelial-to-mesenchymal transition.

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

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):626. doi: 10.1007/s12032-013-0626-4. Epub 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0626-](http://dx.doi.org/10.1007/s12032-013-0626-4)

[4](#)

AUTORES / AUTHORS: - Miao L; Zhu S; Wang Y; Li Y; Ding J; Dai J; Cai H; Zhang D; Song Y

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Nanjing Drum Tower Hospital Affiliated to Medical School of Nanjing University, 321 Zhongshan Road, Nanjing 210008, China.

RESUMEN / SUMMARY: - Discoidin domain receptors (DDR) are a novel class of receptor tyrosine kinases that respond to several collagens and facilitate cell adhesion. DDR1 is highly expressed in a variety of human cancers, and it is clear that DDR1 is primarily expressed in epithelial cells including lung, colon and brain. Moreover, DDR1 expression can be stimulated by collagen types I, II, III, IV, V, VIII and XI, and aberrant signaling induced by DDR1 dysregulated expression is involved in various steps of tumorigenesis. However, the molecular mechanism underlying the role of DDR1 in cancer development is not well documented. In this study, we found that the expression of DDR1 is upregulated in non-small cell lung cancer (NSCLC) tissues and cells when compared with counterpart normal tissues and cells. Furthermore, collagen I could induce DDR1 expression, and activated DDR1 promoted NSCLC cell migration and invasion, while knockdown of DDR1 by transfection with siRNA resulted in a significant decrease in cell migrativeness and invasiveness. Enhanced DDR1 expression mediated by collagen I could activate MMP-2, N-cadherin and vimentin expression, but reduce E-cadherin expression; however, inhibition of DDR1 expression could suppress MMP-2, N-cadherin and vimentin expression and induce E-cadherin activation. In conclusion, our findings indicated that upregulation of DDR1 induced by collagen I may contribute to the development and progression of NSCLC and this effect may be associated with increased invasiveness, at least in part, via promoting epithelial-to-mesenchymal transition.

[560]

TÍTULO / TITLE: - MicroRNA-23^a modulates tumor necrosis factor-alpha-induced osteoblasts apoptosis by directly targeting Fas.

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

REVISTA / JOURNAL: - J Cell Biochem. 2013 Jun 26. doi: 10.1002/jcb.24622.

●● Enlace al texto completo (gratis o de pago) [1002/jcb.24622](http://dx.doi.org/10.1002/jcb.24622)

AUTORES / AUTHORS: - Dong J; Cui X; Jiang Z; Sun J

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedics, Provincial Hospital Affiliated to Shandong University, Jinan, China.

RESUMEN / SUMMARY: - Tumor necrosis factor (TNF)-alpha is a key cytokine regulator of bone and mediates inflammatory bone loss. The molecular

signaling that regulates bone loss downstream of TNF-alpha is poorly defined. Recent studies implicated an important role of microRNAs in TNF-alpha-mediated bone metabolism, including osteoblasts differentiation, osteoclasts differentiation and apoptosis. However, there are very few studies on the complex regulation of microRNAs during TNF-alpha-induced osteoblasts apoptosis. In the present study, the clonal murine osteoblastic cell line, MC3T3-E1, was used. We screened for differentially expressed microRNAs during TNF-alpha induced MC3T3-E1 cell apoptosis and identified microRNA-23^a as a potential inhibitor of apoptosis. To delineate the role of microRNA-23^a in apoptosis, we respectively silenced and overexpressed microRNA-23^a in MC3T3-E1 cells. We found that microRNA-23^a depletion significantly enhances TNF-alpha-induced MC3T3-E1 cell apoptosis and over-expressing microRNA-23^a remarkably attenuates this phenomenon. Mechanistic studies showed that microRNA-23^a inhibits Fas expression through a microRNA-23^a-binding site within the 3'-untranslational region of Fas. The post-transcriptional repression of Fas was further confirmed by luciferase reporter assay. These results showed that microRNA-23^a, an important protecting factor, plays a significant role in the process of TNF-alpha induced MC3T3-E1 cell apoptosis, by regulating Fas expression. J. Cell. Biochem. © 2013 Wiley Periodicals, Inc.

[561]

TÍTULO / TITLE: - Phase I trial of fenretinide delivered orally in a novel organized lipid complex in patients with relapsed/refractory neuroblastoma: A report from the new approaches to neuroblastoma therapy (NANT) consortium.

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

REVISTA / JOURNAL: - Pediatr Blood Cancer. 2013 Jun 29. doi: 10.1002/psc.24643.

●● Enlace al texto completo (gratis o de pago) [1002/psc.24643](#)

AUTORES / AUTHORS: - Maurer BJ; Kang MH; Villablanca JG; Janeba J; Groshen S; Matthay KK; Sondel PM; Maris JM; Jackson HA; Goodarzi F; Shimada H; Czarnecki S; Hasenauer B; Reynolds CP; Marachelian A

INSTITUCIÓN / INSTITUTION: - Department of Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Lubbock, Texas; Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock, Texas; Department of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas.

RESUMEN / SUMMARY: - BACKGROUND: A phase I study was conducted to determine the maximum-tolerated dose, dose-limiting toxicities (DLTs), and pharmacokinetics of fenretinide (4-HPR) delivered in an oral powdered lipid complex (LXS) in patients with relapsed/refractory neuroblastoma. PROCEDURE: 4-HPR/LXS powder (352-2,210 mg/m² /day) was administered on Days 0-6, in 21-day courses, by standard 3 + 3 design. RESULTS: Thirty-two patients (median age = 8 years, range 3-27 years) enrolled with 30

evaluable for dose escalation. Prior therapies included stem cell transplantation/support (n = 26), 13-cis-retinoic acid (n = 22), 125/131 I-MIBG (n = 13), and anti-GD2 antibody (n = 6). 170+ courses were delivered. Course 1 DLTs were a Grade 3 (n = 1) alkaline phosphatase at 352 mg/m² /day. Other major toxicities were Grade 4 (n = 1) alkaline phosphatases on Courses 5 and 6 at 774 mg/m² /day, and Grade 3 (n = 1) ALT/AST elevation on Course 2 at 1,700 mg/m² /day. Of 29 response-evaluable patients, six had stable disease (SD) (4-26 courses); four with marrow- or bone disease-only had complete responses (CR) (10-46 courses). 4-HPR plasma levels were several folds higher (P < 0.05) than previously reported using capsular fenretinide. The Day 6 mean peak 4-HPR plasma level at 1,700 mg/m² /day was 21 microM. An MTD was not reached. CONCLUSIONS: 4-HPR/LXS oral powder obtained higher plasma levels, with minimal toxicity and evidence of anti-tumor activity, than a previous capsule formulation. A recommended phase II schedule of 4-HPR/LXS powder is 1,500 mg/m² /day, TID, on Days 0-6, of a 21-day course. *Pediatr Blood Cancer* 2013;9999:XX-XX. © 2013 Wiley Periodicals, Inc.

[562]

TÍTULO / TITLE: - Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276.

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

REVISTA / JOURNAL: - *Leukemia*. 2013 Jun 11. doi: 10.1038/leu.2013.172.

●● Enlace al texto completo (gratis o de pago) [1038/leu.2013.172](#)

AUTORES / AUTHORS: - Schmidt J; Braggio E; Kortuem KM; Egan JB; Zhu YX; Xin CS; Tiedemann RE; Palmer SE; Garbitt VM; McCauley D; Kauffman M; Shacham S; Chesi M; Bergsagel PL; Stewart AK

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Mayo Clinic, Scottsdale, AZ, USA.

RESUMEN / SUMMARY: - RNA interference screening identified XPO1 (exportin 1) among the 55 most vulnerable targets in multiple myeloma (MM). XPO1 encodes CRM1, a nuclear export protein. XPO1 expression increases with MM disease progression. Patients with MM have a higher expression of XPO1 compared with normal plasma cells (P<0.04) and to patients with monoclonal gammopathy of undetermined significance/smoldering MM (P<0.0001). The highest XPO1 level was found in human MM cell lines (HMCLs). A selective inhibitor of nuclear export compound KPT-276 specifically and irreversibly inhibits the nuclear export function of XPO1. The viability of 12 HMCLs treated with KPT-276 was significantly reduced. KPT-276 also actively induced apoptosis in primary MM patient samples. In gene expression analyses, two genes of probable relevance were dysregulated by KPT-276: cell division cycle 25 homolog A (CDC25A) and bromodomain-containing protein 4 (BRD4), both of which are associated with c-MYC pathway. Western blotting and reverse

transcription-PCR confirm that c-MYC, CDC25A and BRD4 are all downregulated after treatment with KPT-276. KPT-276 reduced monoclonal spikes in the Vk*MYC transgenic MM mouse model, and inhibited tumor growth in a xenograft MM mouse model. A phase I clinical trial of an analog of KPT-276 is ongoing in hematological malignancies including MM. Leukemia advance online publication, 28 June 2013; doi:10.1038/leu.2013.172.

[563]

TÍTULO / TITLE: - Response of Pediatric Uveitis to Tumor Necrosis Factor-alpha Inhibitors.

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

REVISTA / JOURNAL: - J Rheumatol. 2013 Aug;40(8):1394-1403. Epub 2013 Jul 1.

●● Enlace al texto completo (gratis o de pago) [3899/jrheum.121180](#)

AUTORES / AUTHORS: - Lerman MA; Burnham JM; Chang PY; Daniel E; Foster CS; Hennessy S; Jabs DA; Joffe MM; Kacmaz RO; Levy-Clarke GA; Mills MD; Nussenblatt RB; Rosenbaum JT; Suhler EB; Thorne JE; Kempen JH

INSTITUCIÓN / INSTITUTION: - From the Division of Rheumatology, The Children's Hospital of Philadelphia (CHOP), Philadelphia, Pennsylvania; Center for Clinical Epidemiology and Biostatistics, Department of Epidemiology and Biostatistics, Scheie Eye Institute/Department of Ophthalmology, and Perelman School of Medicine (SOM) at the University of Pennsylvania, Philadelphia; Massachusetts Eye Research and Surgery Institution, Ocular Immunology and Uveitis Foundation, Cambridge, Massachusetts; The New York Eye and Ear Infirmary, New York, New York; Harvard Medical School, Boston, Massachusetts; Departments of Medicine and Ophthalmology, Mount Sinai School of Medicine, New York, New York; Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; Department of Ophthalmology, The Johns Hopkins University School of Medicine; Allergan Inc., Irvine, California; The Laboratory of Immunology, National Eye Institute, Bethesda, Maryland; Johnson & Johnson Vision Care, Jacksonville, Florida; Division of Ophthalmology, CHOP; Department of Ophthalmology, and the Division of Rheumatology, Department of Internal Medicine, Oregon Health Sciences University, and the Department of Ophthalmology, Portland Veteran's Affairs Medical Center, Portland, Oregon, USA.

RESUMEN / SUMMARY: - OBJECTIVE: To evaluate the outcome of tumor necrosis factor-alpha inhibition (anti-TNF) for pediatric uveitis. METHODS: We retrospectively assessed children (age \leq 18 yrs) with noninfectious uveitis receiving anti-TNF at 5 uveitis centers and 1 pediatric rheumatology center. Incident treatment success was defined as minimal or no uveitis activity at \geq 2 consecutive ophthalmological examinations \geq 28 days apart while taking no oral and \leq 2 eyedrops/day of corticosteroids. Eligible children had active uveitis and/or were taking higher corticosteroid doses. RESULTS: Among 56

eligible children followed over 33.73 person-years, 52% had juvenile idiopathic arthritis (JIA) and 75% had anterior uveitis (AU). The Kaplan-Meier estimated proportion achieving treatment success within 12 months was 75% (95% CI 62%-87%). Complete absence of inflammatory signs with discontinuation of all corticosteroids was observed in an estimated 64% by 12 months (95% CI 51%-76%). Diagnoses of JIA or AU were associated with greater likelihood of success, as was the oligoarticular subtype among JIA cases. In a multivariable model, compared to those with JIA-associated AU, those with neither or with JIA or AU alone had a 75%-80% lower rate of achieving quiescence under anti-TNF, independent of the number of immunomodulators previously or concomitantly prescribed. Uveitis reactivated within 12 months of achieving quiescence in 14% of those continuing anti-TNF (95% CI 6%-31%). The incidence of discontinuation for adverse effects was 8%/year (95% CI 1%-43%). CONCLUSION: Treatment with anti-TNF was successful and sustained in a majority of children with noninfectious uveitis, and treatment-limiting toxicity was infrequent. JIA-associated AU may be especially responsive to anti-TNF.

[564]

TÍTULO / TITLE: - Histone deacetylase inhibitors activate CIITA and major histocompatibility complex class II antigen expression in diffuse large B cell lymphoma.

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

REVISTA / JOURNAL: - Immunology. 2013 Jun 21. doi: 10.1111/imm.12136.

●● [Enlace al texto completo \(gratis o de pago\) 1111/imm.12136](#)

AUTORES / AUTHORS: - Cycon KA; Mulvaney K; Rimsza LM; Persky D; Murphy SP

INSTITUCIÓN / INSTITUTION: - Zeptomatrix Corp., Buffalo, New York, 14202.

RESUMEN / SUMMARY: - Diffuse large B cell lymphoma (DLBCL), the most common form of non-Hodgkin lymphoma (NHL) diagnosed in the United States, consists of at least two distinct subtypes: germinal center B (GCB) and activated B cell (ABC). Decreased major histocompatibility class II (MHCII) expression on the tumors in both DLBCL subtypes directly correlates with significant decreases in patient survival. One common mechanism accounting for MHCII downregulation in DLBCL is reduced expression of the MHC class II transactivator (CIITA), the master regulator of MHCII transcription. Furthermore, reduced CIITA expression in ABC DLBCL correlates with the presence of the transcriptional repressor positive regulatory domain-1-binding factor-1 (PRDI-BF1). However, the mechanisms underlying downregulation of CIITA in GCB DLBCL are currently unclear. In this study, we demonstrate that neither PRDI-BF1 nor CpG hypermethylation at the CIITA promoters are responsible for decreased CIITA in GCB DLBCL. In contrast, histone modifications associated with an open chromatin conformation and active transcription were significantly lower at the CIITA promoters in CIITA(-) GCB cells compared to CIITA(+) B

cells, which suggests that epigenetic mechanisms contribute to repression of CIITA transcription. Treatment of CIITA(-) or CIITA(low) GCB cells with several different histone deacetylase inhibitors (HDACi) activated modest CIITA and MHCII expression. However, CIITA and MHCII levels were significantly higher in these cells after exposure to the HDAC-1-specific inhibitor MS-275. These results suggest that CIITA transcription is repressed in GCB DLBCL cells through epigenetic mechanisms involving HDACs, and that HDACi treatment can alleviate repression. These observations may have important implications for patient therapy. This article is protected by copyright. All rights reserved.

[565]

TÍTULO / TITLE: - Neurological events with tumour necrosis factor alpha inhibitors reported to the Food and Drug Administration Adverse Event Reporting System.

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

REVISTA / JOURNAL: - Aliment Pharmacol Ther. 2013 Aug;38(4):388-96. doi: 10.1111/apt.12385. Epub 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1111/apt.12385](#)

AUTORES / AUTHORS: - Deepak P; Stobaugh DJ; Sherid M; Sifuentes H; Ehrenpreis ED

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Research Institute, NorthShore University Health System, Evanston, IL, USA.

RESUMEN / SUMMARY: - BACKGROUND: The association between inhibition of tumour necrosis factor alpha (TNF-alpha) and new onset of neurological adverse events (AEs) is unclear. AIMS: To evaluate neurological AEs with TNF-alpha inhibitors reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) utilising a standardised scoring tool for drug-induced AEs. METHODS: A search of FAERS for neurological AEs (January 1, 2000 to December 31, 2009) reported with infliximab, adalimumab, certolizumab and etanercept was performed. Full-text reports were accessed using the Freedom of Information Act and scored using Naranjo score, while accounting for temporal association, previous conclusive reports of the neurological AE with any TNF-alpha inhibitor, and alternate explanations including underlying disease, concomitant medications and comorbidities, such as diabetes mellitus. RESULTS: There were 772 reports. Most were in patients who had rheumatoid arthritis (393, 50.9%) followed by inflammatory bowel disease (140, 18.1%). No significant differences in age or gender were seen between IBD patients compared with rheumatological diseases (P = 0.584 and P = 0.055 respectively). Etanercept was reported most (327, 42.4%) followed by infliximab (276, 35.8%) (P = 0.008). Peripheral neuropathy was the most common neurological AE (296 reports, 38.3%) followed by central nervous system and/or spinal cord demyelination (153 reports, 19.8%). Majority (551, 71.4%) of the reports were of 'possible' AE with the remaining 'probable' AE

and none identified as 'definite' AE. CONCLUSION: While several neurological AEs have been described, definite association between de novo development of these AEs and exposure to TNF-alpha inhibitors was not established using the Naranjo score.

[566]

TÍTULO / TITLE: - Anti-tumor selectivity of a novel Tubulin and HSP90 dual-targeting inhibitor in non-small cell lung cancer models.

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

REVISTA / JOURNAL: - Biochem Pharmacol. 2013 Aug 1;86(3):351-60. doi: 10.1016/j.bcp.2013.05.019. Epub 2013 Jun 3.

●● Enlace al texto completo (gratis o de pago) 1016/j.bcp.2013.05.019

AUTORES / AUTHORS: - Zhang Q; Zhai S; Li L; Li X; Zhou H; Liu A; Su G; Mu Q; Du Y; Yan B

INSTITUCIÓN / INSTITUTION: - School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China.

RESUMEN / SUMMARY: - Dose-limiting toxicity is a main road blocker for successful cancer chemotherapy. By phenotype screening, a novel chemical agent 2-(2-Chlorophenylimino)-5-(4-dimethylamino-benzylidene) thiazolidin-4-one (CDBT) was found to strongly inhibit the proliferation of non-small cell lung cancer (NSCLC) cells H460 and H322 while displaying no obvious toxicity to normal fast-dividing fibroblast cells NHFB and WI-38 at a concentration 100-fold higher than its EC50 to NSCLC cells. CDBT targets microtubule and heat shock protein 90 (HSP90) simultaneously with moderate affinities compared to microtubule targeting Colchicine and HSP90 inhibitor 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG). CDBT blocks microtubule formation, decreases cancer-essential proteins CRAF-1, ERBB2 and phosphorylated AKT, and causes G2/M arrest and apoptosis. The moderate inhibitory effects of CDBT on targets require a higher cellular concentration of targets, a situation only exist in cancer cells. This accounts for its good cancer selectivity. Furthermore, CDBT effectively inhibits tumor growth by 62.4% relative to the vehicle control after i.p. administration at 30mg/kg for 11 days while showing no toxicity to normal tissues in NSCLC H460 xenograft mouse model.

[567]

TÍTULO / TITLE: - Severe Adverse Events from the Treatment of Advanced Melanoma: A Systematic Review of Severe Side Effects Associated with Ipilimumab, Vemurafenib, Interferon Alfa-2b, Dacarbazine, and Interleukin-2.

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

REVISTA / JOURNAL: - J Dermatolog Treat. 2013 Jun 14.

- Enlace al texto completo (gratis o de pago)

[3109/09546634.2013.813897](https://doi.org/10.1093/ajcp/31.09/46634.2013.813897)

AUTORES / AUTHORS: - Ma C; Armstrong A

INSTITUCIÓN / INSTITUTION: - University of California Davis, Dermatology, Sacramento, California, United States.

RESUMEN / SUMMARY: - Abstract Background: Current immunomodulatory agents for stage III and IV melanoma exert different mechanisms of action that manifest in distinct adverse events. Objective: This systematic review aims to synthesize safety data from clinical trials on ipilimumab, vemurafenib, interferon alfa-2b, dacarbazine, and interleukin-2 to elucidate the severe adverse events associated with each melanoma therapy. Methods: Through a systematic search using MEDLINE, EMBASE, and the Cochrane Central Register between January 1, 2010 and June 1, 2012, we identified 32 clinical trials with 5802 subjects that met inclusion criteria. Results: Ipilimumab was associated with immune-mediated diarrhea and colitis, with an incidence rate of 0.0017 cases per 100 person-years. Patients receiving vemurafenib developed keratoacanthomas and cutaneous squamous cell carcinoma at an incidence rate of 0.0025 cases per 100 person-years. Treatment with interferon alfa-2b precipitated depression at an incidence rate of 0.0002 cases per 100 person-years. Dacarbazine was associated with respiratory toxicity and dyspnea, with incidence rates of 0.0001 and 0.00008 cases per 100 person-years, respectively. Interleukin-2 treatment induced vascular leak syndrome, with symptoms of hypotension and oliguria observed at incidence rates of 0.17 and 0.15 cases per 100 person-years, respectively. Findings may serve as a foundation for further research and guide clinical recommendations.

[568]

TÍTULO / TITLE: - A 92-gene cancer classifier predicts the site of origin for neuroendocrine tumors.

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

REVISTA / JOURNAL: - Mod Pathol. 2013 Jul 12. doi: 10.1038/modpathol.2013.105.

- Enlace al texto completo (gratis o de pago)

[1038/modpathol.2013.105](https://doi.org/10.1038/modpathol.2013.105)

AUTORES / AUTHORS: - Kerr SE; Schnabel CA; Sullivan PS; Zhang Y; Huang VJ; Erlander MG; Brachtel EF; Dry SM

INSTITUCIÓN / INSTITUTION: - Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.

RESUMEN / SUMMARY: - A diagnosis of neuroendocrine carcinoma is often morphologically straight-forward; however, the tumor site of origin may remain elusive in a metastatic presentation. Neuroendocrine tumor subtyping has important implications for staging and patient management. In this study, the novel use and performance of a 92-gene molecular cancer classifier for

determination of the site of tumor origin are described in a series of 75 neuroendocrine tumors (44 metastatic, 31 primary; gastrointestinal (n=12), pulmonary (n=22), Merkel cell (n=10), pancreatic (n=10), pheochromocytoma (n=10), and medullary thyroid carcinoma (n=11)). Formalin-fixed, paraffin-embedded samples passing multicenter pathologist adjudication were blinded and tested by a 92-gene molecular assay that predicts tumor type/subtype based upon relative quantitative PCR expression measurements for 87 tumor-related and 5 reference genes. The 92-gene assay demonstrated 99% (74/75; 95% confidence interval (CI) 0.93-0.99) accuracy for classification of neuroendocrine carcinomas and correctly subtyped the tumor site of origin in 95% (71/75; 95% CI 0.87-0.98) of cases. Analysis of gene expression subsignatures within the 92-gene assay panel showed 4 genes with promising discriminatory value for tumor typing and 15 genes for tumor subtyping. The 92-gene classifier demonstrated excellent accuracy for classifying and determining the site of origin in tumors with neuroendocrine differentiation. These results show promise for use of this test to aid in classifying neuroendocrine tumors of indeterminate primary site, particularly in the metastatic setting. Modern Pathology advance online publication, 12 July 2013; doi:10.1038/modpathol.2013.105.

[569]

TÍTULO / TITLE: - PD-0332991, a Potent and Selective Inhibitor of Cyclin-dependent Kinase 4/6, Demonstrates Inhibition of Proliferation in Renal Cell Carcinoma at Nanomolar Concentrations and Molecular Markers Predict for Sensitivity.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Aug;33(8):2997-3004.

AUTORES / AUTHORS: - Logan JE; Mostofizadeh N; Desai AJ; VON Euw E; Conklin D; Konkankit V; Hamidi H; Eckardt M; Anderson L; Chen HW; Ginther C; Taschereau E; Bui PH; Christensen JG; Beldegrun AS; Slamon DJ; Kabbinavar FF

INSTITUCIÓN / INSTITUTION: - Institute of Urologic Oncology, Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, 924 Westwood Blvd., Suite 1050, Los Angeles, CA 90095, U.S.A. Joshuaelogan@gmail.com.

RESUMEN / SUMMARY: - BACKGROUND: PD-0332991 is an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, and was evaluated to determine its anti-proliferative effects in 25 renal cell carcinoma (RCC) cell lines. MATERIALS AND METHODS: Half-maximal inhibitory concentrations (IC50) of PD-0332991 were determined with cell line proliferation assays, as were its effects on the cell cycle, apoptosis, and retinoblastoma (RB) phosphorylation. Molecular markers for response prediction, including p16, p15, cyclin D1 (CCND1), cyclin E1 (CCNE1), E2F transcription factor 1 (E2F1), RB, CDK4 and CDK6, were

studied using array comparative genomic hybridization (CGH) and gene expression. RESULTS: IC50 values for PD-0332991 ranged from 25.0 nM to 700 nM, and the agent demonstrated G0/G1 cell-cycle arrest, induction of late apoptosis, and blockade of RB phosphorylation. Through genotype and expression data p16, p15 and E2F1 were identified as having significant association between loss and sensitivity to PD-0332991: p16 (p=0.021), p15 (p=0.047), and E2F1 (p=0.041). CONCLUSION: PD-0332991 has antiproliferative activity in RCC cell lines, and molecular markers predict for sensitivity to this agent.

[570]

TÍTULO / TITLE: - Cisplatin enhances the efficacy of 5-Aminolevulinic acid mediated photodynamic therapy in human head and neck squamous cell carcinoma.

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

REVISTA / JOURNAL: - Gen Physiol Biophys. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [4149/gpb_2013046](#)

AUTORES / AUTHORS: - Ahn JC; Biswas R; Mondal A; Lee YK; Chung PS

INSTITUCIÓN / INSTITUTION: - Medical Laser Research Center, College of Medicine, Dankook University, Cheonan, Chungnam, Korea.
pschung@dankook.ac.kr.

RESUMEN / SUMMARY: - Photodynamic therapy (PDT) has become a promising option for the treatment of head and neck, and other forms of cancer. 5-Aminolevulinic acid (ALA) is one of the popular photosensitizers used in PDT. It is a heme precursor and is converted to a photosensitizer protoporphyrin IX. In this present study, the combination of anticancer drug cisplatin (CDDP) and ALA mediated PDT was used to study the cytotoxicity in vitro as well as in vivo. Human head and neck cancer cells AMC-HN3 were treated with cisplatin and ALA-mediated PDT individually, and also in combination. Several approaches like confocal microscopic study, cytotoxicity assay etc. have been performed to study the intracellular accumulation of protoporphyrin IX in cells and its effectiveness in PDT, when treated in combination with chemotherapy drug, cisplatin (CDDP). The combination of treatments efficacy was also studied in tumor xenograft model. Compared to the individual treatments, combination of CDDP and PDT was found to be more cytotoxic in AMC-HN3, and also more effective in reducing the tumor volume in mice xenograft. Thus, with the combined therapy, not only the efficacy of treatment can be enhanced, but the doses of the drugs can also be lowered. This in turn can reduce the side effects of the chemotherapy drugs. Therefore, this study may lead to a potential drug-PDT combination that may be a useful treatment modality for human head and neck cancer.

[571]

TÍTULO / TITLE: - Diallyl disulfide suppresses proliferation and induces apoptosis in human gastric cancer through Wnt-1 signaling pathway by up-regulation of miR-200b and miR-22.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jul 9. pii: S0304-3835(13)00492-8. doi: 10.1016/j.canlet.2013.06.027.

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

[1016/j.canlet.2013.06.027](#)

AUTORES / AUTHORS: - Tang H; Kong Y; Guo J; Tang Y; Xie X; Yang L; Su Q; Xie X

INSTITUCIÓN / INSTITUTION: - Department of Breast Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China; State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China; Cancer Research Institute, University of South China, Hengyang, Hunan, People's Republic of China.

RESUMEN / SUMMARY: - The purpose of this study was to identify a mechanism related to miRNA pathway which plays a role in the anti-tumor effects of Diallyl disulfide. Alterations in miRNA expression were observed in Diallyl disulfide-treated MGC-803 cells, including up-regulation of miR-200b and miR-22 expression. Furthermore, Wnt-1 was identified as a target of both miR-200b and miR-22. MiR-200b and miR-22 not only synergistically inhibited gastric cancer growth, but also enhanced the antitumor effect of Diallyl disulfide both in vitro and in vivo. It indicated that miR-200b and miR-22 may serve as potential gene therapy and enhance Diallyl disulfide antitumor effects.

[572]

TÍTULO / TITLE: - Epirubicin-mediated expression of miR-302b is involved in osteosarcoma apoptosis and cell cycle regulation.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Jul 8;222(1):1-9. doi: 10.1016/j.toxlet.2013.06.242.

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

[1016/j.toxlet.2013.06.242](#)

AUTORES / AUTHORS: - Zhang Y; Hu H; Song L; Cai L; Wei R; Jin W

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China.

RESUMEN / SUMMARY: - Epirubicin is widely used in osteosarcoma chemotherapy. Growing evidence indicates that the microRNA (miRNA) expression levels which are induced by chemotherapeutic agents play an important role in osteosarcoma development and progression. In this study we investigate the alterations of miRNA expression in the osteosarcoma cells after

epirubicin treatment and whether miRNAs can enhance its anti-osteosarcoma effect. After epirubicin exposure, microarray shows 40 miRNAs are differentially expressed in osteosarcoma cells including 24 down-regulated miRNAs. Notably, miR-302b, which is stably low-expressed in osteosarcoma, could be induced by the epirubicin. Furthermore, we find that miR-302b can inhibit the osteosarcoma cell proliferation, promote cell apoptosis and cell cycle arrest. MiR-302b can activate caspase-3 and regulate the Akt/pAkt, Bcl-2, Bim expression to increase the cell apoptosis. Meanwhile, miR-302b also attenuates cyclin D1 and CDKs expression to induce cell cycle arrest. Therefore, our results suggest miR-302b can play an essential role in osteosarcoma treatment as a potential tumor suppressor.

[573]

TÍTULO / TITLE: - PBOX-15 induces apoptosis and improves the efficacy of oxaliplatin in human colorectal cancer cell lines.

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

REVISTA / JOURNAL: - Eur J Pharmacol. 2013 Jul 16. pii: S0014-2999(13)00521-9. doi: 10.1016/j.ejphar.2013.07.011.

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

[1016/j.ejphar.2013.07.011](#)

AUTORES / AUTHORS: - Gangemi G; Gaggero P; Fiore D; Proto MC; Butini S; Gemma S; Casagni A; Laezza C; Vitale M; Ligresti A; Di Marzo V; Zisterer DM; Nathwani S; Clive Williams D; Campiani G; Bifulco M

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical and Biomedical Sciences, University of Salerno, 84084 Fisciano, SA, Italy.

RESUMEN / SUMMARY: - An emerging new class of targeted therapeutic molecules against the enzyme fatty acid amide hydrolase (FAAH) is a novel series of pyrrolo-1,5-benzoxa(thia)zepine compounds. A member of this family, pyrrolo-1,5-benzoxazepine-15 (PBOX-15), is a tubulin depolymerizing agent displaying a proapoptotic activity in a variety of human tumor cell types, including those derived from both solid and hematological malignancies, with minimal toxicity towards normal blood and bone marrow cells. In this study, we evaluated the PBOX-15-mediated effects in human colorectal cancer cell (CRC) lines. The compound, used at doses equal to or greater than 1 μM inhibits the proliferation of human CRC cell lines in a dose- and time-dependent manner, inducing a significant cell cycle arrest in the G2/M phase. DNA fragmentation assays and western blot analysis demonstrated that treatments prolonged over 48h triggered a strong activation of the intrinsic apoptotic pathway as indicated by activation of caspase-3, caspase-9 and PARP. Moreover, nanomolar doses of PBOX-15, unable to cause microtubule depolymerization, significantly improved the oxaliplatin and 5-fluorouracil-induced anti-proliferative effects in CRC cell lines. These results showed, for the first time, that PBOX-15

represents a promising compound for the treatment of human CRC and a strong candidate for novel therapeutic options.

[574]

TÍTULO / TITLE: - Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: A new era begins.

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

REVISTA / JOURNAL: - Cancer Treat Rev. 2013 Jul 3. pii: S0305-7372(13)00125-4. doi: 10.1016/j.ctrv.2013.06.002.

●● Enlace al texto completo (gratis o de pago) [1016/j.ctrv.2013.06.002](#)

AUTORES / AUTHORS: - Remon J; Moran T; Majem M; Reguart N; Dalmau E; Marquez-Medina D; Lianes P

INSTITUCIÓN / INSTITUTION: - Medical Oncology Department, Hospital de Mataro, Carretera de la Cirera, s/n, 08304 Mataro, Barcelona, España. Electronic address: jremon@cscdm.cat.

RESUMEN / SUMMARY: - The discovery of mutated oncogenes has opened up a new era for the development of more effective treatments for non-small cell lung cancer patients (NSCLC) harbouring EGFR mutations. However, patients with EGFR-activating mutation ultimately develop acquired resistance (AR). Several studies have identified some of the mechanisms involved in the development of AR to EGFR tyrosine kinase inhibitors (TKI) that can be potential therapeutic strategies, although in up to 30% of cases, the underlying mechanism of AR are still unexplained. In this review we aim to summarize the main mechanisms of AR to EGFR TKI and some clinical strategies that can be used in the daily clinical practice to overcome this resistance and try to prolong the outcomes in this subgroup of patients.

[575]

TÍTULO / TITLE: - Novel methylsulfonyl chalcones as potential antiproliferative drugs for human prostate cancer: Involvement of the intrinsic pathway of apoptosis.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Jul 19. doi: 10.3892/ijo.2013.2024.

●● Enlace al texto completo (gratis o de pago) [3892/ijo.2013.2024](#)

AUTORES / AUTHORS: - Ismail B; Ghezali L; Gueye R; Limami Y; Pouget C; Leger DY; Martin F; Beneytout JL; Duroux JL; Diab-Assaf M; Fagnere C; Liagre B

INSTITUCIÓN / INSTITUTION: - Biochemistry and Molecular Biology Laboratory, Faculty of Pharmacy, University of Limoges, FR 3503 GEIST, EA1069, GDR CNRS 3049, Limoges, France.

RESUMEN / SUMMARY: - Limited success has been achieved in extending the survival of patients with metastatic and hormone-refractory prostate cancer (HRPC). There is a strong need for novel agents in the treatment and prevention of HRPC. In the present study, the apoptotic mechanism of action of RG003 (2'-hydroxy-4-methylsulfonylchalcone) and RG005 (4'-chloro-2'-hydroxy-4-methylsulfonylchalcone) in association with intracellular signalling pathways was investigated in the hormone-independent prostate carcinoma cells PC-3 and DU145. We showed that these compounds induced apoptosis through the intrinsic pathway but not through the extrinsic one. We showed that synthetic chalcones induced an activation of caspase-9 but not caspase-8 in PC-3 cells. Even if both chalcones induced apoptosis in PC-3 cells, a dominant effect of RG003 treatment was observed resulting in a disruption of p53, caspase-9 and caspase-3 activation, PARP cleavage and DNA fragmentation. Furthermore, in regard to our results, it is clear that the simultaneous inhibition of Akt and NF-kappaB signalling can significantly contribute to the anticancer effects of RG003 and RG005 in PC-3 prostate cancer cells. NF-kappaB inhibition was correlated with the reduction of COX-2 expression and induction of apoptosis. Our results clearly indicate for the first time that RG003 and RG005 exert their potent antiproliferative and pro-apoptotic effects through the modulation of Akt/NF-kappaB/COX-2 signal transduction pathways in PC-3 prostate cancer cells with a dominant effect for RG003.

[576]

TÍTULO / TITLE: - RUNX1-ETO induces a type I interferon response which negatively effects t(8;21)-induced increased self-renewal and leukemia development.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 25.

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

[3109/10428194.2013.815351](#)

AUTORES / AUTHORS: - Dekelver RC; Lewin B; Weng S; Yan M; Biggs J; Zhang DE

INSTITUCIÓN / INSTITUTION: - Division of Biological Sciences.

RESUMEN / SUMMARY: - The 8;21 translocation is the most common chromosomal aberration occurring in acute myeloid leukemia (AML). This translocation causes expression of the RUNX1-ETO (AML1-ETO) fusion protein, which cooperates with additional mutations in leukemia development. We report here that interferons (IFNs) and IFN-stimulated genes are a group of genes consistently up-regulated by RUNX1-ETO in both human and murine models. RUNX1-ETO-induced up-regulation of IFN-stimulated genes occurs primarily via type I IFN signaling with a requirement for the IFNAR complex. Addition of exogenous IFN in vitro significantly reduces the increase in self-renewal potential induced by both RUNX1-ETO and its leukemogenic splicing

isoform RUNX1-ETO9a. Finally, loss of type I IFN signaling via knockout of Ifnar1 significantly accelerates leukemogenesis in a t(8;21) murine model. This demonstrates the role of increased IFN signaling as an important factor inhibiting t(8;21) fusion protein function and leukemia development and supports the use of type I IFNs in the treatment of AML.

[577]

TÍTULO / TITLE: - The role of glutamate decarboxylase 65 in gastric cancer development, progression, and prognosis.

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

REVISTA / JOURNAL: - Histopathology. 2013 Apr 17. doi: 10.1111/his.12164.

●● [Enlace al texto completo \(gratis o de pago\) 1111/his.12164](#)

AUTORES / AUTHORS: - Song Y; Li S; Wang Z; Zhu J; Gao P; Wang M; Dong Y; Xu H

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology and General Surgery, First Hospital of China Medical University, Shenyang, China.

RESUMEN / SUMMARY: - AIMS: Recent studies have revealed that glutamate decarboxylase 65 (GAD65) plays important roles in cancer progression. The role of GAD65 in gastric cancer development, progression and prognosis is currently unknown, and we aimed to investigate this. METHODS AND RESULTS: Immunohistochemistry revealed that GAD65 expression in 313 gastric cancer tissues was significantly higher than in 60 adjacent non-tumour tissues. Moreover, the expression level of GAD65 significantly correlated with the depth of tumour invasion and TNM stage. GAD65 expression level was a significant prognostic factor in univariate survival analysis, but did not remain an independent prognostic factor following Cox multivariate analysis. For tumours with an intermediate type growth pattern, when those showing low expression of GAD65 were reclassified with expanding type tumours, and those showing high expression with infiltrative type tumours, there was a significant difference in prognosis between these two novel subgroups, and this remained a significant prognostic factor in multivariate analysis. CONCLUSIONS: Our findings indicate that GAD65 is involved in the development and progression of gastric cancer as a tumour oncoprotein. Further elucidation of the molecular mechanisms underlying the role of GAD65 is warranted.

[578]

TÍTULO / TITLE: - Tyrosine kinase inhibitors (TKIs) in human and pet tumours with special reference to breast cancer: A comparative review.

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

REVISTA / JOURNAL: - Crit Rev Oncol Hematol. 2013 Jun 12. pii: S1040-8428(13)00103-0. doi: 10.1016/j.critrevonc.2013.05.009.

- Enlace al texto completo (gratis o de pago)

[1016/j.critrevonc.2013.05.009](https://doi.org/10.1016/j.critrevonc.2013.05.009)

AUTORES / AUTHORS: - Ranieri G; Pantaleo M; Piccinno M; Roncetti M; Mutinati M; Marech I; Patruno R; Rizzo A; Sciorsci RL

INSTITUCIÓN / INSTITUTION: - Interventional Radiology Unit with Integrated Section of Translational Medical Oncology National Cancer Research Centre, Cancer Institute "Giovanni Paolo II", Bari, Italy. Electronic address: giroan@tiscalinet.it.

RESUMEN / SUMMARY: - Tyrosine kinase receptors (TKRs) play a key role in tumour cell proliferation and survival since they are involved in endothelial cell activation leading to tumour neoangiogenesis. In particular, vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (c-KitR), and colony-stimulating factor 1 (CSF-1) are overexpressed or constitutively activated in human and pet malignancies. A variety of small molecule inhibitors targeting specific tyrosine kinases (known as tyrosine kinase inhibitors or TKIs) have recently been approved, or are under investigation, for the treatment of human cancer. TKI application in animal cancer is however relatively recent. This review aims to illustrate the major aspects of tyrosine kinase dysfunctions, with special regard to human and animal cancer of the mammary gland, providing an update on the background of the anti-angiogenic and anti-neoplastic properties of TKIs in human and veterinary cancer.

[579]

TÍTULO / TITLE: - Autocrine human growth hormone increases sensitivity of mammary carcinoma cell to arsenic trioxide-induced apoptosis.

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

REVISTA / JOURNAL: - Mol Cell Endocrinol. 2013 Jul 10;377(1-2):84-92. doi: 10.1016/j.mce.2013.07.002.

- Enlace al texto completo (gratis o de pago) [1016/j.mce.2013.07.002](https://doi.org/10.1016/j.mce.2013.07.002)

AUTORES / AUTHORS: - Zekri A; Ghaffari SH; Yousefi M; Ghanizadeh-Vesali S; Mojarrad M; Alimoghaddam K; Ghavamzadeh A

INSTITUCIÓN / INSTITUTION: - Hematology, Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran; Department of Medical Genetics, Tehran University of Medical Sciences, Tehran, Iran.

RESUMEN / SUMMARY: - Human growth hormone (hGH) has been increasingly implicated in a variety of cancers; its up-regulation is observed in breast cancer and correlates with a poor outcome. Autocrine hGH promotes mammary carcinoma cell survival, proliferation, immortalization; it confers an invasive phenotype as a result of an epithelial-mesenchymal transition and contributes to chemoresistance and radioresistance. Arsenic trioxide (ATO) is being successfully used as a first and second line therapy for the treatment of patients

with acute promyelocytic leukemia. It also inhibits tumor cell growth and induces apoptosis in a broad range of solid tumors. In the present study, we investigated the effect of hGH on sensitivity of a mammary adenocarcinoma cell to ATO, using a stable hGH-transfectant MCF-7 cell line, MCF7-hGH. Our results demonstrated for the first time that the overexpression of hGH increased sensitivity of the breast cancer cell line MCF-7 to ATO through apoptotic and anti-proliferative mechanisms. The effect of ATO on the transcriptional level of genes involved in survival (Bcl-2, Bax and Survivin), self-sufficiency in growth signals (c-Myc, ARF, Cdc25A, p53 and Bax), immortalization (hTERT) and invasion and metastasis (MMP-2 and MMP-9, uPA and uPAR and E-cadherin) was more pronounced in MCF7-hGH compared with its parental MCF-7 line. Our study may highlight the potential application of ATO for the treatment of patients with breast cancer, especially in those who have metastatic and chemoresistant tumor phenotype possibly due to the over expression of hGH.

[580]

TÍTULO / TITLE: - UGT1A1 genotype-specific phase I and pharmacokinetic study for combination chemotherapy with irinotecan and cisplatin: a Saitama Tumor Board study.

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

REVISTA / JOURNAL: - Eur J Gynaecol Oncol. 2013;34(2):120-3.

AUTORES / AUTHORS: - Takano M; Goto T; Hirata J; Furuya K; Horie K; Takahashi M; Yokota H; Kino N; Kudoh K; Kikuchi Y

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Japan. mastkn@ndmc.ac.jp

RESUMEN / SUMMARY: - INTRODUCTION: Genotyping of UGT1A1 could be useful for prediction of severe toxicities for patients treated with irinotecan; however, genotype-based recommended dose (RD) has not been established. The aim of the present study was to determine the RD of irinotecan in combination with cisplatin (CPT-P) for individuals with or without UGT1A1 polymorphisms. MATERIALS AND METHODS: According to polymorphisms of UGT1A1*28, *6, and *27, RDs were determined by three-case cohort methods for patients with wild-type and heterotype, and by inter-patient dose escalation for homotype patients. Pharmacokinetic studies were also evaluated. During May 2009 and July 2011, 18 Japanese patients were enrolled; 16 patients with ovarian carcinoma, and two cases with cervical cancer. The RD of irinotecan was determined as 50 mg/m² for the patients with wild-type, 40 mg/m² for those with heterotype, and 30 mg/m² for homotype UGT 1A1 genotype. RESULTS: Patients with homotype UGT1A1 alleles had a significantly lower glucuronidation ratio in comparison with UGT1A1 wild-type and heterotype cases. CONCLUSION: UGT1A1 genotype-based RDs of irinotecan in CPT-P therapy were determined. Further studies to investigate efficacy of the RD including response evaluation are needed to confirm the present results.

[581]

TÍTULO / TITLE: - The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials.

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

REVISTA / JOURNAL: - Ann Oncol. 2013 Jun 20.

●● Enlace al texto completo (gratis o de pago) [1093/annonc/mdt226](#)

AUTORES / AUTHORS: - Lyman GH; Dale DC; Culakova E; Poniewierski MS; Wolff DA; Kuderer NM; Huang M; Crawford J

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Duke University, Durham.

RESUMEN / SUMMARY: - BACKGROUND: The granulocyte colony-stimulating factor (G-CSF) is utilized to reduce neutropenic complications in patients receiving cancer chemotherapy. This study represents a systematic review and evidence summary of the impact of G-CSF support on chemotherapy dose intensity and overall mortality. MATERIALS AND METHODS: All randomized controlled trials (RCTs) comparing chemotherapy with or without G-CSF support and reporting all-cause mortality with at least 2 years of follow-up were sought. Dual-blind data abstraction of disease, treatment, patient and outcome study results with conflict resolution by third party was carried out. RESULTS: The search revealed 61 randomized comparisons of chemotherapy with or without initial G-CSF support. Death was reported in 4251 patients randomized to G-CSFs and in 5188 controls. Relative risk (RR) with G-CSF support for all-cause mortality was 0.93 (95% confidence interval: 0.90-0.96; P < 0.001). RR for mortality varied by intended chemotherapy dose and schedule: same dose and schedule (RR = 0.96; P = 0.060), dose dense (RR = 0.89; P < 0.001), dose escalation (RR = 0.92; P = 0.019) and drug substitution or addition (RR = 0.94; P = 0.003). Greater RR reduction was observed among studies with longer follow-up (P = 0.02), where treatment was for curative intent (RR = 0.91; P < 0.001), and where survival was the primary outcome (RR = 0.91; P < 0.001). CONCLUSIONS: All-cause mortality is reduced in patients receiving chemotherapy with primary G-CSF support. The greatest impact was observed in RCTs in patients receiving dose-dense schedules.

[582]

TÍTULO / TITLE: - Brown seaweed fucoidan: Biological activity and apoptosis, growth signaling mechanism in cancer.

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

REVISTA / JOURNAL: - Int J Biol Macromol. 2013 Sep;60:366-74. doi: 10.1016/j.ijbiomac.2013.06.030. Epub 2013 Jun 28.

- Enlace al texto completo (gratis o de pago)

[1016/j.ijbiomac.2013.06.030](https://doi.org/10.1016/j.ijbiomac.2013.06.030)

AUTORES / AUTHORS: - Senthilkumar K; Manivasagan P; Venkatesan J; Kim SK

INSTITUCIÓN / INSTITUTION: - Marine Bioprocess Research Center, Pukyong National University, Busan 608-737, Republic of Korea. Electronic address: senthilbhus@gmail.com.

RESUMEN / SUMMARY: - Seaweeds, being abundant sources of bioactive components have much interest in recent times. The complex polysaccharides from the brown, red and green seaweeds possess broad spectrum therapeutic properties. The sulfated polysaccharides are routinely used in biomedical research and have known biological activities. Fucoidan, a fucose-rich polysaccharide extracted from brown seaweed has various biological functions including anticancer effects. Cellular damage induces growth arrest and tumor suppression by inducing apoptosis, the mechanism of cell death depends on the magnitude of DNA damage following exposure to anticancer agents. Apoptosis is mainly regulated by cell growth signaling molecules. Number of research studies evidenced that fucoidan shown to induce cytotoxicity of various cancer cells, induces apoptosis, and inhibits invasion, metastasis and angiogenesis of cancer cells. There are few articles discussing on fucoidan biological activity but no specific review on cancer and its signaling mechanism. Hence, this review discusses the brown seaweed fucoidan structure and some biological function and role in apoptosis, invasion, metastasis, angiogenesis and growth signal mechanism on cancer.

[583]

TÍTULO / TITLE: - CT Perfusion Can Predict Overexpression of CXCL8 (Interleukin-8) in Head and Neck Squamous Cell Carcinoma.

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

REVISTA / JOURNAL: - AJNR Am J Neuroradiol. 2013 Jul 4.

- Enlace al texto completo (gratis o de pago) [3174/ajnr.A3610](https://doi.org/10.3174/ajnr.A3610)

AUTORES / AUTHORS: - Jo SY; Wang PI; Nor JE; Bellile EL; Zhang Z; Worden FP; Srinivasan A; Mukherji SK

INSTITUCIÓN / INSTITUTION: - Departments of Radiology, Otolaryngology, and Medical Oncology, and Cancer Center Biostatistics Unit, University of Michigan Hospital, Ann Arbor, Michigan; and Angiogenesis Research Laboratory, Department of Restorative Sciences, University of Michigan School of Dentistry, Ann Arbor, Michigan.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Increased angiogenesis in head and neck squamous cell carcinoma correlates to more aggressive tumors with increased morbidity. Because both elevated blood flow and high serum CXCL8 levels are correlated with increased angiogenesis, our objective was to see if elevated blood flow measured with CT perfusion correlated with CXCL8 levels, thereby helping to identify candidates for targeted

therapies that inhibit the Bcl-2 proangiogenic pathway associated with CXCL8. MATERIALS AND METHODS: Seven patients with locally recurrent or metastatic head and neck squamous cell carcinoma were enrolled in the trial. These patients underwent CT perfusion and the following parameters were measured: blood volume, blood flow, capillary permeability, and MTT; relative values were calculated by dividing by normal-appearing muscle. Serum was drawn for CXCL8 enzyme-linked immunosorbent assay analysis in these patients. RESULTS: There was a significant positive correlation between the CXCL8 levels and relative blood flow ($r = 0.94$; $P = .01$). No correlation was found between CXCL8 and relative blood volume, relative capillary permeability, or relative MTT. CONCLUSIONS: Relative blood flow may be useful as a surrogate marker for elevated CXCL8 in patients with head and neck squamous cell cancer. Patients with elevated relative blood flow may benefit from treatment targeting the Bcl-2 proangiogenic pathways.

[584]

TÍTULO / TITLE: - Rapamycin interacts synergistically with idarubicin to induce T-leukemia cell apoptosis in vitro and in a mesenchymal stem cell simulated drug-resistant microenvironment via Akt/mammalian target of rapamycin and extracellular signal-related kinase signaling pathways.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jun 7.

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

[3109/10428194.2013.811579](#)

AUTORES / AUTHORS: - Wu KN; Zhao YM; He Y; Wang BS; Du KL; Fu S; Hu KM; Zhang LF; Liu LZ; Hu YX; Wang YJ; Huang H

RESUMEN / SUMMARY: - Abstract T-cell acute lymphoblastic leukemias (T-ALLs) are clonal lymphoid malignancies with poor prognosis, and still lack of effective treatment. Here we examined the interactions between the mammalian target of rapamycin (mTOR) inhibitor rapamycin and idarubicin (IDA) in series of human T-ALL cell lines Molt-4, Jurkat, CCRF-CEM, and CEM/C1. Co-exposure of cells to rapamycin and IDA synergistically induced T-ALL cells growth inhibition and apoptosis mediated by caspase activation via intrinsic mitochondrial pathway and extrinsic pathway, Combined treatment with rapamycin and IDA down-regulate Bcl-2 and Mcl-1, inhibit the activation of PI3K/ mTOR and extracellular signal-related kinase (ERK). They also played synergistic pro-apoptotic roles in the drug-resistant microenvironment simulated by mesenchymal stem cells (MSCs) as a feeder layer. In addition, MSCs protect T-ALL cells from IDA cytotoxicity by up-regulating ERK phosphorylation, while rapamycin efficiently reversed this protective effect. Taken together, we confirm the synergistic antitumor effects of rapamycin and IDA, and provide an insight into the potential future clinical applications of combined rapamycin-IDA regimens for treating T-cell malignancies.

[585]

TÍTULO / TITLE: - microRNA-1 Induces Growth Arrest and Apoptosis in Malignant Mesothelioma.

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

REVISTA / JOURNAL: - Chest. 2013 Jul 4. doi: 10.1378/chest.12-2770.

●● Enlace al texto completo (gratis o de pago) [1378/chest.12-2770](#)

AUTORES / AUTHORS: - Xu Y; Zheng M; Merritt RE; Shrager JB; Wakelee H; Kratzke RA; Hoang CD

RESUMEN / SUMMARY: - ABSTRACT BACKGROUND: We investigated microRNA expression profiles of malignant pleural mesothelioma (MPM) specimens to identify novel microRNA that are potentially involved in the oncogenic transformation of human pleural cells. METHODS: microRNA microarray transcriptional profiling studies of 25 MPM primary tumors were performed. We used normal pleural from an unmatched patient cohort as normal comparators. To confirm microarray data, we used real-time quantitative PCR. Representative cell lines H513 and H2052 were used in functional analyses of microRNA-1. RESULTS: In addition to several novel MPM-associated microRNAs, we observed that the expression level of microRNA-1 was significantly lower in tumors as compared to normal pleural specimens. Subsequently, pre-mir of microRNA-1 was introduced into MPM cell lines to overexpress this microRNA. Phenotypic changes of these altered cells were assayed. The cellular proliferation rate was significantly inhibited after overexpression of microRNA-1. Early and late apoptosis was increased markedly in microRNA-1-transfected cell lines. Taken together, these data suggested that overexpression of microRNA-1 induced apoptosis in these MPM cell lines, acting as a tumor suppressor. We confirmed our observations by assessing in the transduced MPM cells cell cycle-related genes, pro-apoptotic and anti-apoptotic genes, which all showed coordinated, significant changes characteristic of the apoptotic phenotype. CONCLUSIONS: Thus, further investigation and validation of our microRNA database of MPM may elucidate previously unrecognized molecular pathways and/ or mechanisms by identifying novel microRNAs that are involved in malignant transformation. Our study has now found microRNA-1 to be one of these MPM-associated microRNAs, with potential pathogenic and therapeutic significance.

[586]

TÍTULO / TITLE: - Revisiting DNA damage repair, p53-mediated apoptosis and cisplatin sensitivity in germ cell tumors.

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

REVISTA / JOURNAL: - Int J Dev Biol. 2013;57(2-3-4):273-280.

●● Enlace al texto completo (gratis o de pago) [1387/ijdb.130135mb](#)

AUTORES / AUTHORS: - Cavallo F; Feldman DR; Barchi M

INSTITUCIÓN / INSTITUTION: - Department of Biomedicine and Prevention, University of Rome Tor Vergata, Italy. marco.barchi@uniroma2.it.

RESUMEN / SUMMARY: - Testicular germ cell tumors (TGCTs), ie, seminomas and nonseminomas, account for 1% to 3% of all neoplasms in men. They are the most common cancer in young white males and are unique in their responsiveness to cisplatin-based chemotherapy. For this reason, TGCTs are considered a model for curative disease. However, up to now, the molecular mechanisms behind this exceptional responsiveness to DNA-damaging agents have remained unclear. A hypersensitive apoptotic response, as well as a reduction in the proficiency to repair cisplatin-induced DNA damage might account for this behavior. In this review, building on recent findings of p53-induced apoptosis and DNA-repair mechanisms in TGCTs, we will discuss the molecular bases that drive tumor sensitivity to cisplatin, emphasizing the new therapeutic approaches proposed to eventually constrain tumor recurrence, and target TGCTs which are unresponsive to standard therapies.

[587]

TÍTULO / TITLE: - Anti-apoptotic role of the sonic hedgehog signaling pathway in the proliferation of ameloblastoma.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Sep;43(3):695-702. doi: 10.3892/ijo.2013.2010. Epub 2013 Jul 8.

●● Enlace al texto completo (gratis o de pago) 3892/ijo.2013.2010

AUTORES / AUTHORS: - Kanda S; Mitsuyasu T; Nakao Y; Kawano S; Goto Y; Matsubara R; Nakamura S

INSTITUCIÓN / INSTITUTION: - Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan.

RESUMEN / SUMMARY: - Sonic hedgehog (SHH) signaling pathway is crucial to growth and patterning during organogenesis. Aberrant activation of the SHH signaling pathway can result in tumor formation. We examined the expression of SHH signaling molecules and investigated the involvement of the SHH pathway in the proliferation of ameloblastoma, the most common benign tumor of the jaws. We used immunohistochemistry on ameloblastoma specimens and immunocytochemistry and reverse transcription-PCR on the ameloblastoma cell line AM-1. We also used the inhibitors of SHH signaling, SHH neutralizing antibody and cyclopamine, to assess the effects of SHH on the proliferation of AM-1 cells. We detected expression of SHH, patched, GLI1, GLI2 and GLI3 in the ameloblastoma specimens and AM-1 cells. The proliferation of these cells was significantly inhibited in the presence of SHH neutralizing antibody or cyclopamine; this was confirmed by BrdU incorporation assays. Furthermore, in the presence of SHH neutralizing antibody, nuclear translocation of GLI1 and

GLI2 was abolished, apoptosis was induced, BCL-2 expression decreased and BAX expression increased. Our results suggest that the SHH signaling pathway is constitutively active in ameloblastoma and plays an anti-apoptotic role in the proliferation of ameloblastoma cells through autocrine loop stimulation.

[588]

TÍTULO / TITLE: - Synergistic interactions between camptothecin and EGFR or RAC1 inhibitors and between imatinib and Notch signaling or RAC1 inhibitors in glioblastoma cell lines.

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

REVISTA / JOURNAL: - Cancer Chemother Pharmacol. 2013 Aug;72(2):329-40. doi: 10.1007/s00280-013-2197-7. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1007/s00280-013-2197-](#)

[7](#)

AUTORES / AUTHORS: - Sooman L; Ekman S; Andersson C; Kultima HG; Isaksson A; Johansson F; Bergqvist M; Blomquist E; Lennartsson J; Gullbo J

INSTITUCIÓN / INSTITUTION: - Rudbeck Laboratory, Department of Radiation, Oncology and Radiation Science, Section of Oncology, Uppsala University, Dag Hammarskjölds väg 20, 751 85, Uppsala, Sweden, linda.sooman@onkologi.uu.se.

RESUMEN / SUMMARY: - **PURPOSE:** The current treatment strategies for glioblastoma have limited health and survival benefits for the patients. A common obstacle in the treatment is chemoresistance. A possible strategy to evade this problem may be to combine chemotherapeutic drugs with agents inhibiting resistance mechanisms. The aim with this study was to identify molecular pathways influencing drug resistance in glioblastoma-derived cells and to evaluate the potential of pharmacological interference with these pathways to identify synergistic drug combinations. **METHODS:** Global gene expressions and drug sensitivities to three chemotherapeutic drugs (imatinib, camptothecin and temozolomide) were measured in six human glioblastoma-derived cell lines. Gene expressions that correlated to drug sensitivity or resistance were identified and mapped to specific pathways. Selective inhibitors of these pathways were identified. The effects of six combinations of inhibitors and chemotherapeutic drugs were evaluated in glioblastoma-derived cell lines. Drug combinations with synergistic effects were also evaluated in non-cancerous epithelial cells. **RESULTS:** Four drug combinations had synergistic effects in at least one of the tested glioblastoma-derived cell lines; camptothecin combined with gefitinib (epidermal growth factor receptor inhibitor) or NSC 23766 (ras-related C3 botulinum toxin substrate 1 inhibitor) and imatinib combined with DAPT (Notch signaling inhibitor) or NSC 23766. Of these, imatinib combined with DAPT or NSC 23766 did not have synergistic effects in non-cancerous epithelial cells. Two drug combinations had at least additive effects in one of the tested glioblastoma-derived cell lines; temozolomide

combined with gefitinib or PF-573228 (focal adhesion kinase inhibitor).
CONCLUSION: Four synergistic and two at least additive drug combinations were identified in glioblastoma-derived cells. Pathways targeted by these drug combinations may serve as targets for future drug development with the potential to increase efficacy of currently used/evaluated chemotherapy.

[589]

TÍTULO / TITLE: - The overexpression of P21-activated kinase 5 (PAK5) promotes paclitaxel-chemoresistance of epithelial ovarian cancer.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1767-](#)

[7](#)

AUTORES / AUTHORS: - Li D; Yao X; Zhang P

INSTITUCIÓN / INSTITUTION: - Department of Gynecology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, 200092, People's Republic of China.

RESUMEN / SUMMARY: - P21-activated kinase 5 (PAK5) is the recently identified member of the group II p21-activated kinases (PAKs) family, which is characterized by a highly conserved amino-terminal Cdc42/Rac interactive binding domain and a carboxyl terminal kinase domain. However, the role of PAK5 in gynecological cancers has not been evaluated so far. It is remarkable that we found PAK5 was overexpressed in epithelial ovarian cancer (EOC), which is faced with an obstacle of paclitaxel resistance. Therefore, in this study, we aim to examine the PAK5 expression during EOC progression, the role of PAK5 in malignant progression of EOC and the probable relationship between PAK5 and EOC paclitaxel resistance. By immunohistochemistry, our results showed that PAK5 expression was increased with EOC progression through the adenoma to carcinoma sequence, with the highest expression level in invasive and metastatic EOCs. Furthermore, the expression level of PAK5 was also found to increase in accordance with the development of EOC Federation International of Gynecology and Obstetrics stages ($P = 0.038$) and differentiation grades ($P = 0.008$). Remarkably, those patients who recurred within 6 months after accepting tumor reductive surgery and the following carboplatin + paclitaxel chemotherapy had the highest PAK5 expression ($P = 0.015$). Moreover, in in vitro studies, we found that SK-OV-3 cell growth was decreased while paclitaxel chemosensitivity was correspondingly increased with the down-regulation of PAK5. Taken together, our study demonstrated that PAK5 is correlated to human EOC and increased PAK5 expression promotes EOC progression, and PAK5 regulates EOC cell paclitaxel chemoresistance.

[590]

TÍTULO / TITLE: - The value of gadoteric acid-enhanced and diffusion-weighted MRI for prediction of grading of pancreatic neuroendocrine tumors.

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

REVISTA / JOURNAL: - Acta Radiol. 2013 Jul 29.

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

[1177/0284185113494982](#)

AUTORES / AUTHORS: - Jang KM; Kim SH; Lee SJ; Choi D

INSTITUCIÓN / INSTITUTION: - Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

RESUMEN / SUMMARY: - BACKGROUND: Parenchyma-preserving resection for the treatment of benign pancreatic neuroendocrine tumors (NETs) has been tried, and preoperative prediction of benign pancreatic NET is important. Recently, diffusion-weighted imaging (DWI) of abdomen magnetic resonance imaging (MRI) has been used to characterize benign and malignant tumors and DWI might be helpful in prediction of benign pancreatic NETs. PURPOSE: To evaluate the value of gadoteric acid-enhanced MRI and DWI in predicting benign pancreatic NETs for determination of parenchyma-preserving resection. MATERIAL AND METHODS: Our ethics committee approved this study with a waiver of informed consent given its retrospective design. We searched radiology and pathology databases from November 2010 to July 2012 to identify patients who underwent surgery for pancreatic NETs (<4 cm). Twenty patients in the benign group and 14 patients in the non-benign group were included in this study. Two radiologists analyzed the morphologic features, signal intensity on MR images including DWI (b = 800), and dynamic enhancement pattern of the tumors with consensus. The tumor-to-parenchyma ratio and tumor apparent diffusion coefficients (ADCs) were quantitatively assessed. RESULTS: The benign pancreatic NETs were more often round (7/20, 35%) or ovoid (13/20, 65%) in shape and less hypovascular on the arterial phase (3/20, 15%) than were the non-benign pancreatic NETs (1/14, 7.1% and 5/14, 35.8%; 7/14, 50% respectively; P < 0.05). Main pancreatic duct dilatation by tumors was demonstrated only in non-benign pancreatic NETs (4/14, 28.4%; P = 0.021). ADC values and ratios were significantly different between benign pancreatic NETs (mean, 1.48×10^{-3} mm²/sec, 1.11 ± 0.25 , each) and non-benign pancreatic NETs (mean, 1.04×10^{-3} mm²/sec, 0.74 ± 0.13 , each) (P < 0.01). Other qualitative and quantitative analyses between benign and non-benign pancreatic NETs were not significantly different (P > 0.05). CONCLUSION: Abdominal MRI with DWI may be useful for differentiating benign pancreatic NETs from non-benign pancreatic NETs, which might be helpful for determination of parenchyma-preserving resection.

[591]

TÍTULO / TITLE: - Three missense mutations of DNA topoisomerase I in highly camptothecin-resistant colon cancer cell sublines.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 5. doi: 10.3892/or.2013.2594.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2594](#)

AUTORES / AUTHORS: - Arakawa Y; Ozaki K; Okawa Y; Yamada H

INSTITUCIÓN / INSTITUTION: - Department of Oncology and Hematology, Jikei University School of Medicine, MinatoKu, Tokyo 1058471, Japan.

RESUMEN / SUMMARY: - Various anticancer drugs, including camptothecins and indolocarbazoles, target DNA topoisomerase I (Top1). We previously described the camptothecin-resistant colon cancer cell line DLDSNR6, which has a Gly365Ser missense mutation in Top1. In the present study, we established highly camptothecin-resistant sublines from DLDSNR6 cells by continuous exposure to higher camptothecin concentrations. The established sublines grew in the presence of 30 microM of camptothecin, but exhibited markedly retarded growth. In addition to Gly365Ser, these sublines harbored a Top1 Gly717Arg mutation and some had also a Top1 Gln421Arg mutation. Top1 activity was reduced to approximately one-eighth in highly resistant cell lines compared with that in parental DLD-1 cells. Resistant clones with 3 Top1 mutations including Gln421RArg exhibited the highest resistance to the indolocarbazole J-107088 in terms of the effect on the cell cycle distribution. The Gln421 mutation was equivalent to a mutation recently found in camptothecin biosynthesizing plants, but it has not previously been found in mammalian cells.

[592]

TÍTULO / TITLE: - Tumor vessel depiction with contrast-enhanced endoscopic ultrasonography predicts efficacy of chemotherapy in pancreatic cancer.

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

REVISTA / JOURNAL: - Pancreas. 2013 Aug;42(6):990-5. doi: 10.1097/MPA.0b013e31827fe94c.

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

[1097/MPA.0b013e31827fe94c](#)

AUTORES / AUTHORS: - Yamashita Y; Ueda K; Itonaga M; Yoshida T; Maeda H; Maekita T; Iguchi M; Tamai H; Ichinose M; Kato J

INSTITUCIÓN / INSTITUTION: - From the Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan.

RESUMEN / SUMMARY: - **OBJECTIVES:** Contrast-enhanced endoscopic ultrasonography (CE-EUS) is a new imaging modality for pancreatic lesions. The aim of this study was to evaluate if CE-EUS is useful for predicting treatment efficacy before pancreatic cancer chemotherapy by assessing intratumoral vessel flow. **METHODS:** Thirty-nine patients with unresectable advanced pancreatic cancer underwent CE-EUS before chemotherapy. The patients were divided into 2 groups according to the intratumoral vessel flow

observed with CE-EUS: vessel sign-positive and vessel sign-negative groups. Patient prognosis was investigated according to presence or absence of the vessel sign. RESULTS: Two patients were excluded due to poor visualization of CE-EUS images; therefore, 37 patients were analyzed. Contrast-enhanced EUS revealed positive vessel sign in 20 patients, whereas it revealed negative vessel sign in 17 patients. Both progression-free survival and overall survival were significantly longer in the positive- versus negative vessel sign groups ($P = 0.037$ and $P = 0.027$, respectively). Multivariate analysis demonstrated that the positive vessel sign was an independent factor associated with longer overall survival (hazard ratio, 0.22; 95% confidence interval, 0.08-0.53). CONCLUSIONS: Evaluation of intratumoral vessel flow by CE-EUS could be useful for predicting efficacy of chemotherapy in patients with pancreatic cancer. Contrast-enhanced EUS could be used before chemotherapy for inoperable pancreatic cancer.

[593]

TÍTULO / TITLE: - Let-7b expression determines response to chemotherapy through the regulation of Cyclin D1 in Glioblastoma.

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

REVISTA / JOURNAL: - J Exp Clin Cancer Res. 2013 Jun 27;32(1):41. doi: 10.1186/1756-9966-32-41.

●● Enlace al texto completo (gratis o de pago) [1186/1756-9966-32-41](#)

AUTORES / AUTHORS: - Guo Y; Yan K; Fang J; Qu Q; Zhou M; Chen F

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Xiangya Hospital, Central South University, 410008, Changsha, China.

fenghuachen2013@sina.cn.

RESUMEN / SUMMARY: - BACKGROUND: Glioblastoma is the most common type of primary brain tumors. Cisplatin is a commonly used chemotherapeutic agent for Glioblastoma patients. Despite a consistent rate of initial responses, cisplatin treatment often develops chemoresistance, leading to therapeutic failure. Cellular resistance to cisplatin is of great concern and understanding the molecular mechanisms is an utter need. METHODS: Glioblastoma cell line U251 cells were exposed to increasing doses of cisplatin for 6 months to establish cisplatin-resistant cell line U251R. The differential miRNA expression profiles in U251 and U251R cell lines were identified by microarray analysis and confirmed by Q-PCR. MiRNA mimics were transfected into U251R cells, and cellular response to cisplatin-induced apoptosis and cell cycle distribution were examined by FACS analysis. RESULTS: U251R cells showed 3.1-fold increase in cisplatin resistance compared to its parental U251 cells. Microarray analysis identified Let-7b and other miRNAs significantly down-regulated in U251R cells compared to U251 cells. Transfection of Let-7b mimics greatly re-sensitized U251R cells to cisplatin, while transfection of other miRNAs has no effect or slightly effect. Cyclin D1 is predicted as a target of Let-7b through bioinformatics

analysis. Over-expression of Let-7b mimics suppressed cyclin D1 protein expression and inhibited cyclin D1-3'-UTR luciferase activity. Knockdown of cyclin D1 expression significantly increased cisplatin-induced G1 arrest and apoptosis. CONCLUSIONS: Collectively, our results indicated that cisplatin treatment leads to Let-7b suppression, which in turn up-regulates cyclin D1 expression. Let-7b may serve as a marker of cisplatin resistance, and can enhance the therapeutic benefit of cisplatin in glioblastoma cells.

[594]

TÍTULO / TITLE: - Concomitant Interferon-alpha and Chemotherapy in Hepatitis C and Colorectal Cancer: A Case Report.

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

REVISTA / JOURNAL: - In Vivo. 2013 Jul-Aug;27(4):527-9.

AUTORES / AUTHORS: - Gentile I; DE Stefano A; DI Flumeri G; Buonomo AR; Carlomagno C; Morisco F; DE Placido S; Borgia G

INSTITUCIÓN / INSTITUTION: - Department of Clinical Medicine and Surgery - Section of Infectious Diseases (Ed. 18), University of Naples Federico II, Via S. Pansini 5, I-80131 Naples, Italy. ivan.gentile@unina.it.

RESUMEN / SUMMARY: - Hepatitis C virus (HCV) infection is one of the main causes of liver disease worldwide. Patients undergoing surgery are at risk of acquiring acute HCV infection and those undergoing surgical eradication of a neoplasia may be indicated for adjuvant treatment. Therefore, unlike chronic infection, these patients may simultaneously need antiviral therapy with interferon for acute hepatitis C and cytotoxic chemotherapy. To date, no data are available regarding the efficacy and tolerability of concomitant interferon treatment and antineoplastic chemotherapy in the setting of acute hepatitis C treatment. Here, we report the case of a 60-year-old man who developed acute hepatitis C after left hemicolectomy for an adenocarcinoma. He received concomitant antiviral treatment with interferon-alpha and adjuvant chemotherapy with capecitabine and oxaliplatin. Both treatments were well-tolerated and the patient completed the scheduled therapies. HCV infection was eradicated and the patient is free of neoplastic disease two years and 6 months after surgery.

[595]

TÍTULO / TITLE: - Indices of initial hepatitis C virus RNA reduction rate to predict efficacy of interferon-beta followed by peginterferon plus ribavirin for genotype 1b high viral load.

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

REVISTA / JOURNAL: - Hepatol Res. 2013 Jun 7. doi: 10.1111/hepr.12182.

●● Enlace al texto completo (gratis o de pago) [1111/hepr.12182](#)

AUTORES / AUTHORS: - Okushin H; Yamamoto T; Kishida H; Morii K; Uesaka K

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Himeji Red Cross Hospital, Himeji-shi, Hyogo, Japan.

RESUMEN / SUMMARY: - AIM: Initial hepatitis C virus (HCV) RNA reduction was investigated as a potential index for sustained virological response (SVR) in the treatment of interferon (IFN)-beta followed by peginterferon plus ribavirin (PEG IFN/RBV). METHODS: The treatment course was retrospectively analyzed in 64 genotype 1b patients with a HCV RNA level of 5.0 logIU/mL or higher. IFN-beta was administered twice a day for 2 weeks followed by 24 or 48 weeks of PEG IFN/RBV. The serum HCV RNA level was measured by real-time polymerase chain reaction before administration and at 1, 2 and 4 weeks of therapy.

RESULTS: By the duration of PEG IFN administration, the SVR rates were 11% (2/18, <19 weeks), 64% (23/36, 20-24 weeks) and 40% (4/10, 25-72 weeks) (P = 0.0011, chi2 -test). The SVR rate was high in patients in whom the HCV RNA level had decreased by 2.5 logIU/mL or greater at 1 week of IFN-beta (29/55 [53%] vs 0/9 [0%], P = 0.0029, chi2 -test). Among these patients, the SVR rate was even higher in those with continuous reduction in the first 2 weeks after the switch to PEG IFN/RBV (27/45 [60%] vs 2/10 [20%], P = 0.0048). Age below 65 years, no previous IFN course and good initial HCV RNA reduction were significantly associated with SVR on multivariate analysis, and the SVR rate was 95% (18/19) among these patients. CONCLUSION: The 2.5 logIU/mL reduction in HCV RNA at 1 week of IFN-beta and the continuous reduction just after the switch to PEG IFN/RBV are important SVR-predictive indices.

[596]

TÍTULO / TITLE: - The Prognostic Impact of Absolute Lymphocyte and Monocyte Counts at Diagnosis of Diffuse Large B-Cell Lymphoma in the Rituximab Era.

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

REVISTA / JOURNAL: - Acta Haematol. 2013 Jul 11;130(4):242-246.

●● Enlace al texto completo (gratis o de pago) [1159/000350484](#)

AUTORES / AUTHORS: - Aoki K; Tabata S; Yonetani N; Matsushita A; Ishikawa T

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Clinical Immunology, Kobe City Medical Center General Hospital, Kobe, Japan.

RESUMEN / SUMMARY: - Background: A recent report showed that the combination of the absolute lymphocyte count (ALC) and the absolute monocyte count (AMC) at diagnosis gave a prognostic score in diffuse large B-cell lymphoma (DLBCL). However, this model requires validation in other patient cohorts. Methods: We retrospectively evaluated the prognostic impact of the combination of the ALC and the AMC at diagnosis in a cohort of 299 DLBCL patients who were treated in the rituximab era at a single institution. Results: In univariate analyses, an ALC $\leq 1.0 \times 10^9/l$ [4-year overall survival (OS) rate 47.0 vs. 79.4%; $p < 0.001$] and an AMC $\geq 0.63 \times 10^9/l$ (4-year OS rate 52.4 vs. 75.6%; $p < 0.001$) were associated with inferior OS, respectively. In multivariate analyses, an ALC $\leq 1.0 \times 10^9/l$ and an AMC $\geq 0.63 \times 10^9/l$ were

significantly associated with inferior OS independently of the International Prognostic Index. Furthermore, the combination of ALC and AMC could identify patients with the dismal prognosis; the 4-year OS rates for patients with ALC $\leq 1.0 \times 10^9/l$ and AMC $\geq 0.63 \times 10^9/l$ were 18.8%. Conclusions: The combination of ALC and AMC at diagnosis may be useful for the prognostic stratification of patients with DLBCL.

[597]

TÍTULO / TITLE: - Combination chemotherapy of nafamostat mesylate with gemcitabine for gallbladder cancer targeting nuclear factor-kappaB activation.

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

REVISTA / JOURNAL: - J Surg Res. 2013 Jun 25. pii: S0022-4804(13)00592-1. doi: 10.1016/j.jss.2013.06.003.

●● Enlace al texto completo (gratis o de pago) [1016/j.jss.2013.06.003](#)

AUTORES / AUTHORS: - Iwase R; Haruki K; Fujiwara Y; Furukawa K; Shiba H; Uwagawa T; Misawa T; Ohashi T; Yanaga K

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Jikei University School of Medicine, Tokyo, Japan; Department of Gene Therapy, Institute of DNA Medicine, Jikei University School of Medicine, Tokyo, Japan. Electronic address: ryotaiwa@jikei.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: Gemcitabine is an effective chemotherapeutic agent for advanced gallbladder cancer. However, chemoresistance attributable to gemcitabine-induced nuclear factor-kappaB (NF-kappaB) activation has been reported. We previously reported that nafamostat mesylate inhibited NF-kappaB activation and induced apoptosis in pancreatic cancer. Therefore, we hypothesized that nafamostat mesylate inhibits gemcitabine-induced NF-kappaB activation and enhances apoptosis induced by gemcitabine in gallbladder cancer. MATERIALS AND METHODS: In vitro, we assessed NF-kappaB activation of a gallbladder cancer cell line (NOZ) treated with nafamostat mesylate, gemcitabine, or a combination of both. In vivo, we established a xenograft gallbladder cancer model in mice by subcutaneous injection of NOZ cells. Five weeks after implantation, the animals were treated with nafamostat mesylate three times a week in the nafamostat mesylate group, with gemcitabine once a week in the gemcitabine group, or with a combination of nafamostat mesylate three times a week and gemcitabine once a week in the combination group, respectively. In the control group, only the vehicle of gemcitabine and nafamostat mesylate was injected at the same time course. RESULTS: In the combination group, NF-kappaB activation was inhibited and apoptosis was enhanced compared with gemcitabine alone in vitro and vivo. Tumor growth in the combination group was significantly slower than that in the gemcitabine group ($P < 0.001$). At the end of the study, the tumor weight and volume in the combination group were significantly lower than those in the gemcitabine group ($P = 0.039$ and 0.028 , respectively). CONCLUSIONS:

Combination chemotherapy of gemcitabine with nafamostat mesylate enhances the anti-tumor effect against xenograft gallbladder cancer model in mice.

[598]

TÍTULO / TITLE: - Texture analysis of advanced non-small cell lung cancer (NSCLC) on contrast-enhanced computed tomography: prediction of the response to the first-line chemotherapy.

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

REVISTA / JOURNAL: - Eur Radiol. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1007/s00330-013-2965-](#)

[0](#)

AUTORES / AUTHORS: - Ravanelli M; Farina D; Morassi M; Roca E; Cavalleri G; Tassi G; Maroldi R

INSTITUCIÓN / INSTITUTION: - Department of Radiology, University of Brescia, Brescia, Italy, marcoravanelli@hotmail.it.

RESUMEN / SUMMARY: - **OBJECTIVES:** To assess whether tumour heterogeneity, quantified by texture analysis (TA) on contrast-enhanced computed tomography (CECT), can predict response to chemotherapy in advanced non-small cell lung cancer (NSCLC). **METHODS:** Fifty-three CECT studies of patients with advanced NSCLC who had undergone first-line chemotherapy were retrospectively reviewed. Response to chemotherapy was evaluated according to RECIST1.1. Tumour uniformity was assessed by a TA method based on Laplacian of Gaussian filtering. The resulting parameters were correlated with treatment response and overall survival by multivariate analysis. **RESULTS:** Thirty-one out of 53 patients were non-responders and 22 were responders. Average overall survival was 13 months (4-35), minimum follow-up was 12 months. In the adenocarcinoma group (n = 31), the product of tumour uniformity and grey level (GL*U) was the unique independent variable correlating with treatment response. Dividing the GL*U (range 8.5-46.6) into tertiles, lesions belonging to the second and the third tertiles had an 8.3-fold higher probability of treatment response compared with those in the first tertile. No association between texture features and response to treatment was observed in the non-adenocarcinoma group (n = 22). GL*U did not correlate with overall survival. **CONCLUSIONS:** TA on CECT images in advanced lung adenocarcinoma provides an independent predictive indicator of response to first-line chemotherapy. **KEY POINTS:** * Contrast enhanced computed tomography is currently used to stage lung cancer. * Texture analysis allows tumour heterogeneity to be quantified on CT images. * Texture parameters seem to predict chemotherapy response in advanced NSCLC.

[599]

TÍTULO / TITLE: - V8, a newly synthetic flavonoid, induces apoptosis through ROS-mediated ER stress pathway in hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Arch Toxicol. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1007/s00204-013-1085-](#)

[6](#)

AUTORES / AUTHORS: - Zhang Y; Zhao L; Li X; Wang Y; Yao J; Wang H; Li F; Li Z; Guo Q

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Carcinogenesis and Intervention, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing, 210009, People's Republic of China.

RESUMEN / SUMMARY: - Natural flavonoids from plants have been demonstrated to possess promising chemopreventive activities against various diseases. 7-{4-[Bis-(2-hydroxy-ethyl)-amino]-butoxy}-5-hydroxy-8-methoxy-2-phenyl-chromen-4-one (V8), a newly synthesized derivative of wogonin may have antioxidant, antiviral, anti-inflammatory and anti-tumor potentials as wogonin. Based on the recent findings of V8, the anti-tumor activities and fundamental mechanisms by which V8 inhibits growth of hepatocellular carcinoma were further investigated in this study. After the treatment of V8, a significant inhibition of HepG2 cell proliferation was observed in a dose-dependent manner with the IC50 value of 23 μM using MTT assay. The exposure to V8 also resulted in apoptosis induction and an accumulation of ROS and Ca²⁺. Meanwhile, a release of cytochrome c (Cyt-c), activation of BH-3 only proteins and Bax, decrease in mitochondrial membrane potential DeltaPsi, as well as a suppression of Bcl-2, pro-caspase9 and pro-caspase3 expression were shown. Moreover, knocking down CHOP partly decreased the effect of V8-mediated apoptosis and activation of GRP78, p-PERK, p-eIF2alpha, ATF4 and CHOP modulated ER stress triggered by V8. In vivo, V8 inhibited the transplanted mice H22 liver carcinomas in a dose-dependent manner. Compared with wogonin, V8 exhibited stronger anti-proliferative effects both in vitro and in vivo. The underlying mechanism of activating PERK-eIF2alpha-ATF4 pathway by which V8 induces apoptosis was verified once again in vivo. The apoptosis induction via the mitochondrial pathway by modulating the ROS-mediated ER signaling pathway might serve to provide support for further studies of V8 as a possible anticancer drug in the clinical treatment of cancer.

PTPTPTP - JOURNAL ARTICLE ----- [600]

TÍTULO / TITLE: - CHD8 is an independent prognostic indicator that regulates Wnt/beta-catenin signaling and the cell cycle in gastric cancer.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 8. doi: 10.3892/or.2013.2597.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2597](#)

AUTORES / AUTHORS: - Sawada G; Ueo H; Matsumura T; Uchi R; Ishibashi M; Mima K; Kurashige J; Takahashi Y; Akiyoshi S; Sudo T; Sugimachi K; Doki Y; Mori M; Mimori K

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Beppu Hospital, Kyushu University, Beppu 874-0838, Japan.

RESUMEN / SUMMARY: - The chromodomain helicase DNA-binding (CHD) family comprises a class of chromatin remodeling enzymes. Previous studies suggest that CHD8 may negatively regulate various genes and signaling pathways, such as the Wnt/betacatenin pathway. However, few studies have investigated the role of CHD8 in cancer cells. We analyzed the expression of CHD8 in cancer lesions and corresponding non-cancerous tissues to demonstrate the prognostic significance of CHD8 expression in 101 cases of gastric cancer. We also investigated the functional implications of aberrant CHD8 expression by conducting gene set enrichment analysis (GSEA). Expression of CHD8 mRNA was significantly lower in gastric cancer tissues compared to that in corresponding normal tissues (P=0.003). In multivariate analysis for overall survival, we found that CHD8 expression was an independent prognostic factor in gastric cancer. Moreover, GSEA revealed that CHD8 was significantly associated with genes involved in the Wnt/betacatenin pathway and in the cell cycle. In addition, knockdown of CHD8 expression in the gastric cancer cell lines, MKN45 and NUGC4, promoted proliferation. In conclusion, the present study suggests that loss of CHD8 expression may be a novel indicator for biological aggressiveness in gastric cancer.

[601]

TÍTULO / TITLE: - Prophylactic thyroidectomy for MEN 2-related medullary thyroid carcinoma based on predictive testing for RET proto-oncogene mutation and basal serum calcitonin in China.

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

REVISTA / JOURNAL: - Eur J Surg Oncol. 2013 Jul 9. pii: S0748-7983(13)00425-3. doi: 10.1016/j.ejso.2013.06.015.

●● Enlace al texto completo (gratis o de pago) 1016/j.ejso.2013.06.015

AUTORES / AUTHORS: - Qi XP; Zhao JQ; Du ZF; Yang RR; Ma JM; Fei J; Cheng J; Han JS; Jin HY; Chen ZG; Wang JQ; Yang YP; Ying RB; Chen XL; Liu WT; Zhao Y; Jiang HL; Zhang XN

INSTITUCIÓN / INSTITUTION: - Department of Oncologic and Urologic Surgery, Clinical Experimental Center and Department of Pathology, The 117th PLA Hospital, 40 Jichang Road, Hangzhou, Zhejiang Province 310004, China. Electronic address: qxplmd@vip.sina.com.

RESUMEN / SUMMARY: - INTRODUCTION: Early and normative surgery is the only curative method for multiple endocrine neoplasia type 2 (MEN 2)-related medullary thyroid carcinoma (MTC). AIMS: To study the timing of prophylactic total thyroidectomy (TT) for MEN 2-related MTC with different RET mutations in

a Chinese population, and to compare the sensitivity and accuracy of fully-automated chemiluminescence immunoassay (FACLIA) and radioimmunoassay (RIA) for serum calcitonin (Ct). METHODS: We collected 24 asymptomatic individuals from 8 unrelated Chinese families with MEN 2, and analyzed RET mutation and Ct levels. Then we performed TT on 17 of the 24 individuals, including TT (2/17), TT with bilateral level VI lymph-node dissection (B-LND(VI); 12/17) and TT with B-LND(VI) + modified unilateral/bilateral/local neck dissection (3/17). RESULTS: Histopathology revealed bilateral/unilateral MTC in 15/17 (88.2%; median diameter, 1.0 cm) and bilateral C-cell hyperplasia in 2/17 (11.8%; p.V292M/R67H/R982C and p.C618Y). Lymph-node metastasis/fibro-adipose tissue invasion (p.C634R) or solely fibro-adipose tissue invasion (p.C634Y) were found in 2/17 (11.8%). Elevated pre-surgical Ct (pre-Ct) was identified by FACLIA in 17/17 (median age, 24.0), while pre-Ct by RIA was found in only 6/15 ($P < 0.001$). The median follow-up was 22.0 months, during which 16/17 had no abnormality (one p.C634R individual had elevated Ct), and another 7 carriers still had consistently undetectable Ct by FACLIA. CONCLUSIONS: Our study highlights the importance and feasibility of individualized prophylactic TT for MEN 2-related MTC, based on predictive integrated screening of RET and pre-Ct levels. Besides, we recommend FACLIA to measure Ct for earlier diagnosis, treatment and follow-up monitoring of MTC.

[602]

TÍTULO / TITLE: - Sorafenib sensitizes hepatocellular carcinoma cell to cisplatin via suppression of Wnt/beta-catenin signaling.

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

REVISTA / JOURNAL: - Mol Cell Biochem. 2013 Sep;381(1-2):139-44. doi: 10.1007/s11010-013-1695-6. Epub 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [1007/s11010-013-1695-6](#)

[6](#)

AUTORES / AUTHORS: - Wei Y; Shen N; Wang Z; Yang G; Yi B; Yang N; Qiu Y; Lu J

INSTITUCIÓN / INSTITUTION: - The Fifth Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Systemic chemotherapy plays an important role in the treatment of patients with advanced liver cancer. However, chemoresistance to cisplatin is a major limitation of cisplatin-based chemotherapy in the clinic, and the underlying mechanism of such resistance is not fully understood. In this study, we found that nuclear accumulation of beta-catenin was higher in cisplatin-resistant Huh7 cells than in Huh7 cells, indicating that Wnt signaling was activated in cisplatin-resistant cells. Wnt

signaling inhibition increased cisplatin-induced growth inhibition in hepatoma cell. We further demonstrated that sorafenib could inhibit Wnt signaling in Huh7 cells and cisplatin-resistant Huh7 cells. Co-treatment with cisplatin and sorafenib was more effective in inhibiting cancer cell proliferation than cisplatin alone in vitro and in vivo, whereas Wnt3a (Wnt activator) treatment abrogated sorafenib-induced growth inhibition. These data demonstrated that sorafenib sensitizes human HCC cell to cisplatin via suppression of Wnt/beta-catenin signaling, thus offering a new target for chemotherapy of HCC.

[603]

TÍTULO / TITLE: - Benzylmorpholine Analogs as Selective Inhibitors of Lung Cytochrome P450 2^a13 for the Chemoprevention of Lung Cancer in Tobacco Users.

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

REVISTA / JOURNAL: - Pharm Res. 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [1007/s11095-013-1054-](#)

[Z](#)

AUTORES / AUTHORS: - Blake LC; Roy A; Neul D; Schoenen FJ; Aube J; Scott EE

INSTITUCIÓN / INSTITUTION: - Department of Medicinal Chemistry, University of Kansas, 1251 Wescoe Hall Dr., Lawrence, Kansas, 66045, USA.

RESUMEN / SUMMARY: - PURPOSE: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), one of the most prevalent and procarcinogenic compounds in tobacco, is bioactivated by respiratory cytochrome P450 (CYP) 2^a13, forming DNA adducts and initiating lung cancer. CYP2A13 inhibition offers a novel strategy for chemoprevention of tobacco-associated lung cancer. METHODS: Twenty-four analogs of a 4-benzylmorpholine scaffold identified by high throughput screening were evaluated for binding and inhibition of both functional human CYP2A enzymes, CYP2A13 and the 94%-identical hepatic CYP2A6, whose inhibition is undesirable. Thus, selectivity is a major challenge in compound design. RESULTS: A key feature resulting in CYP2A13-selective binding and inhibition was substitution at the benzyl ortho position, with three analogs being >25-fold selective for CYP2A13 over CYP2A6. CONCLUSIONS: Two such analogs were negative for genetic and hERG toxicities and metabolically stable in human lung microsomes, but displayed rapid metabolism in human liver and in mouse and rat lung and liver microsomes, likely due to CYP2B-mediated degradation. A specialized knockout mouse mimicking the human lung demonstrates compound persistence in lung and provides an appropriate test model. Compound delivered by inhalation may be effective in the lung but rapidly cleared otherwise, limiting systemic exposure.

[604]

TÍTULO / TITLE: - Effects of lysophosphatidic acid on tumor necrosis factor alpha and interferon gamma action in the bovine corpus luteum.

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

REVISTA / JOURNAL: - Mol Cell Endocrinol. 2013 Jul 13;377(1-2):103-111. doi: 10.1016/j.mce.2013.07.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.mce.2013.07.005](#)

AUTORES / AUTHORS: - Woclawek-Potocka I; Kowalczyk-Zieba I; Tylingo M; Boruszewska D; Sinderewicz E; Skarzynski DJ

INSTITUCIÓN / INSTITUTION: - Department of Reproductive Immunology and Pathology, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, 10-747 Olsztyn, Poland. Electronic address: i.woclawek-potocka@pan.olsztyn.pl.

RESUMEN / SUMMARY: - We examined the effects of LPA on TNFalpha and IFNgamma - induced decrease of P4 synthesis and on the cytokine - induced apoptosis of the cultured luteal cells. In the steroidogenic luteal cells LPA reversed the inhibitory effect of TNFalpha and IFNgamma on P4 synthesis and also inhibited the stimulatory effects of TNFalpha and IFNgamma on the expression of Bax, TNFR1, Fas and FasL as well as caspase 3 activity. These results suggest that TNFalpha and IFNgamma cannot induce apoptosis in the presence of LPA, which orientates the steroidogenic luteal cells towards the survival state. In conclusion our results indicate that LPA supports P4 synthesis and action in the bovine CL.

[605]

TÍTULO / TITLE: - Mitochondrial cytochrome c oxidase subunit II variations predict adverse prognosis in cytogenetically normal acute myeloid leukaemia.

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

REVISTA / JOURNAL: - Eur J Haematol. 2013 Jul 4. doi: 10.1111/ejh.12166.

●● Enlace al texto completo (gratis o de pago) [1111/ejh.12166](#)

AUTORES / AUTHORS: - Silkjaer T; Nyvold CG; Juhl-Christensen C; Hokland P; Norgaard JM

INSTITUCIÓN / INSTITUTION: - Department of Haematology, Aarhus University Hospital, Aarhus, Denmark.

RESUMEN / SUMMARY: - Alterations in the two catalytic genes Cytochrome c oxidase subunit I and II (COI, COII) have recently been suggested to have an adverse impact on prognosis in AML patients. In order to explore this in further detail, we sequenced these two mitochondrial genes in diagnostic bone marrow or blood samples in 235 AML patients. In 37 (16%) patients, a non-synonymous variation in either COI or COII could be demonstrated. No patients harboured both COI and COII non-synonymous variations. Twenty-four (10%) patients had non-synonymous variations in COI, whereas 13 (6%) patients had non-synonymous variations in COII. The COI and COII are essential subunits of cytochrome c oxidase which is the terminal enzyme in the oxidative

phosphorylation complexes (OXPHOS). In terms of disease course, we observed that in patients with a normal cytogenetic analysis at disease presentation (CN-AML) treated with curative intent, the presence of a non-synonymous variation in the COII was an adverse prognostic marker for both overall survival and disease-free survival (DFS) in both univariate (DFS; Hazard ratio (HR) 4.4, P=0.006) and multivariate analyses (DFS; HR 7.2, P=0.001). This is the first demonstration of a mitochondrial aberration playing an adverse prognostic role in adult AML and we argue that its role as a potentially novel adverse prognostic marker in the subset of CN-AML should be explored further. This article is protected by copyright. All rights reserved.

[606]

TÍTULO / TITLE: - Carbonic anhydrase IX: A promising diagnostic and prognostic biomarker in breast carcinoma.

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

REVISTA / JOURNAL: - Acta Histochem. 2013 Jun 28. pii: S0065-1281(13)00108-6. doi: 10.1016/j.acthis.2013.05.009.

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

[1016/j.acthis.2013.05.009](#)

AUTORES / AUTHORS: - Furjelova M; Kovalska M; Jurkova K; Horacek J; Carbolova T; Adamkov M

INSTITUCIÓN / INSTITUTION: - Department of Histology and Embryology, Jessenius Faculty of Medicine, Comenius University, Mala Hora 4, 03601 Martin, Slovakia; Department of Medical Biochemistry, Jessenius Faculty of Medicine, Comenius University, Mala Hora 4, 03601 Martin, Slovakia. Electronic address: martina.furjelova@gmail.com.

RESUMEN / SUMMARY: - We examined the expression of carbonic anhydrase IX (CA IX) by immunohistochemical staining using monoclonal antibody M75 (Institute of Virology, Slovak Academy of Sciences, Bratislava) in a group of 38 fibroadenomas and 55 carcinomas of the breast. In each case, the intensity of staining, percentage of labeled cells and subcellular localization of CA IX were assessed. CA IX was detected in 11/38 fibroadenomas (28.9%). Weak cytoplasmic positivity was dominant in these positive cases. Immunohistochemical analysis of 55 carcinomas showed CA IX expression in 34 cases (61.8%). Membrane staining alone was observed in 27/55 carcinomas (49.1%), while cytoplasmic positivity was found in 4/55 cases (7.3%). Combined membrane and cytoplasmic immunostaining of CA IX was detected in 3/55 carcinomas (5.4%). The intensity of immunoreactivity varied from weak to strong. Under 50% of reactive cells were found in 9/38 fibroadenomas (23.6%) and in 29/55 carcinomas (52.7%). More than 50% of reactive cells were found in 2/38 fibroadenomas (5.3%) and in 5/55 carcinomas (9.1%). Statistical analysis confirmed significant differences in the subcellular localization, intensity of immunoreactivity and percentage of labeled cells in fibroadenomas and

carcinomas ($p < 0.05$). Our results confirmed the hypothesis that expression of CA IX may represent a valuable tumor biomarker as well as a promising diagnostic and prognostic parameter in breast cancer.

[607]

TÍTULO / TITLE: - Selective cellular uptake and induction of apoptosis of cancer-targeted selenium nanoparticles.

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

REVISTA / JOURNAL: - Biomaterials. 2013 Sep;34(29):7106-16. doi: 10.1016/j.biomaterials.2013.04.067. Epub 2013 Jun 22.

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

1016/j.biomaterials.2013.04.067

AUTORES / AUTHORS: - Huang Y; He L; Liu W; Fan C; Zheng W; Wong YS; Chen T

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, Jinan University, Guangzhou 510632, China.

RESUMEN / SUMMARY: - Selenium nanoparticles (SeNPs) have garnered a great deal of attention as potential cancer therapeutic payloads. However, the in vivo targeting drug delivery has been challenging. Herein, we describe the synthesis of transferrin (Tf)-conjugated SeNPs and its use as a cancer-targeted drug delivery system to achieve enhanced cellular uptake and anticancer efficacy. Tf as targeting ligand significantly enhances the cellular uptake of doxorubicin (DOX)-loaded SeNPs through clathrin-mediated and caveolae/lipid raft-mediated endocytosis in cancer cells overexpressing transferrin receptor, and increases their selectivity between cancer and normal cells. DOX-loaded and Tf-conjugated SeNPs (Tf-SeNPs) exhibits unprecedented enhanced cytotoxicity toward cancer cells through induction of apoptosis with the involvement of intrinsic and extrinsic pathways. Internalized Tf-SeNPs triggers intracellular ROS overproduction, thus activates p53 and MAPKs pathways to promote cell apoptosis. In the nude mice xenograft experiment, Tf-SeNPs significantly inhibits the tumor growth via induction of p53-mediated apoptosis. This cancer-targeted design of SeNPs opens a new path for synergistic treating of cancer with higher efficacy and decreased side effects.

[608]

TÍTULO / TITLE: - MicroRNA 181^a improves proliferation and invasion, suppresses apoptosis of osteosarcoma cell.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1007/s13277-013-0902-](http://1007/s13277-013-0902-0)

[0](#)

AUTORES / AUTHORS: - Jianwei Z; Fan L; Xiancheng L; Enzhong B; Shuai L; Can L

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Affiliated Hospital of Nantong University, 20 Xishi Road, Nantong, 226001, Jiangsu Province, People's Republic of China, zhujianwei_nt@163.com.

RESUMEN / SUMMARY: - MicroRNA 181^a (miR-181^a) was found dysregulated in a variety of human cancers and significantly associated with clinical outcome of cancer patients. However, the direct role of miR-181^a has not yet been characterized in osteosarcoma progression. This study was aimed at investigating the effects of miR-181^a on osteosarcoma cell biological behavior. First, the expression of miR-181^a in osteosarcoma cell lines (MG63, HOS, SaOS-2, and U2OS) and a human osteoblastic cell line (hFOB1.19) was detected by qRT-PCR. Results showed that miR-181^a was overexpressed in osteosarcoma cell lines compared to human osteoblastic cell line (hFOB1.19). To investigate the effects of miR-181^a on proliferation, apoptosis, and invasion of osteosarcoma cells, we generated human osteosarcoma MG63 cells in which miR-181^a was either overexpressed or depleted. The MG63 cell viability, cycle, apoptosis, and invasive ability were analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide staining, propidium iodide (PI) staining, Annexin V-FITC/PI double staining, and Transwell invasion experiment, respectively. The results showed that MG63 cell viability, proliferation, and invasive abilities were suppressed, and the apoptosis was enhanced in the group with underexpression of miR-181^a. The viability, proliferation, and invasive abilities were improved, and the apoptosis was inhibited in the group with overexpression of miR-181^a. The results from Western blotting indicated that miR-181^a might be associated with the up-regulation of bcl-2 and matrix metalloproteinase 9 and the down-regulation of tissue inhibitor of metalloproteinases-3 and p21 in MG63 cells. Taken together, our results suggested that miR-181^a might facilitate proliferation and invasion and suppress apoptosis of osteosarcoma cells, which might be a potential target for the treatment of osteosarcoma.

[609]

TÍTULO / TITLE: - Enhanced anti-tumor and anti-angiogenic efficacy of a novel liposomal fenretinide on human neuroblastoma.

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

REVISTA / JOURNAL: - J Control Release. 2013 Jun 19;170(3):445-451. doi: 10.1016/j.jconrel.2013.06.015.

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

1016/j.jconrel.2013.06.015

AUTORES / AUTHORS: - Di Paolo D; Pastorino F; Zuccari G; Caffa I; Loi M; Marimpietri D; Brignole C; Perri P; Cilli M; Nico B; Ribatti D; Pistoia V; Ponzoni M; Pagnan G

INSTITUCIÓN / INSTITUTION: - Experimental Therapies Unit, Laboratory of Oncology, Istituto Giannina Gaslini, 16148 Genoa, Italy.

RESUMEN / SUMMARY: - Neuroblastoma is an embryonal tumor originating from the simpatico-adrenal lineage of the neural crest. It approximately accounts for about 15% of all pediatric oncology deaths. Despite advances in multimodal therapy, metastatic neuroblastoma tumors at diagnosis remain a clinical challenge. Retinoids are a class of compounds known to induce both terminal differentiation and apoptosis/necrosis of neuroblastoma cells. Among them, fenretinide (HPR) has been considered one of the most promising anti-tumor agent but it is partially efficacious due to both poor aqueous solubility and rapid metabolism. Here, we have developed a novel HPR formulation, by which the drug was encapsulated into sterically stabilized nanoliposomes (NL[HPR]) according to the Reverse Phase Evaporation method. This procedure led to a higher structural integrity of liposomes in organic fluids for a longer period of time, in comparison with our previous liposomal formulation developed by the film method. Moreover, NL[HPR] were further coupled with NGR peptides for targeting the tumor endothelial cell marker, aminopeptidase N (NGR-NL[HPR]). Orthotopically xenografted neuroblastoma-bearing mice treated with NGR-NL[HPR] lived statistically longer than mice untreated or treated with free HPR (NGR-NL[HPR] vs both control and HPR: $P < 0.0001$). Also, NL[HPR] resulted in a statistically improved survival (NL[HPR] vs both control and HPR: $P < 0.001$) but to a less extent if compared with that obtained with NGR-NL[HPR] (NGR-NL[HPR] vs NL[HPR]: $P < 0.01$). Staining of tumor sections with antibodies specific for neuroblastoma and for either pericytes or endothelial cells evidenced that HPR reduced neuroblastoma growth through both anti-tumor and anti-angiogenic effects, mainly when delivered by NGR-NL[HPR]. Indeed, in this group of mice a marked reduction of tumor progression, of intra-tumoral vessel counts and VEGF expression, together with a marked down-modulation of matrix metalloproteinases MMP2 and MMP9, was observed. In conclusion, the use of this novel targeted delivery system for the apoptotic and antiangiogenic drug, fenretinide, could be considered as an adjuvant tool in the future treatment of neuroblastoma patients.

[610]

TÍTULO / TITLE: - Extra-thoracic tumor burden but not thoracic tumor burden on (18)F-FDG PET/CT is an independent prognostic biomarker for extensive-disease small cell lung cancer.

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

REVISTA / JOURNAL: - Lung Cancer. 2013 Aug;81(2):218-25. doi: 10.1016/j.lungcan.2013.05.001. Epub 2013 May 31.

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

1016/j.lungcan.2013.05.001

AUTORES / AUTHORS: - Oh JR; Seo JH; Hong CM; Jeong SY; Lee SW; Lee J; Min JJ; Song HC; Bom HS; Kim YC; Ahn BC

INSTITUCIÓN / INSTITUTION: - Department of Nuclear Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea.

RESUMEN / SUMMARY: - **PURPOSE:** The aim of this study was to evaluate the relationship and difference in prognostic significance between whole-body tumor burden, thoracic tumor burden, and extra-thoracic tumor burden on (18)F-FDG PET/CT for patients with extensive-disease small cell lung cancer (ED-SCLC). **MATERIALS AND METHODS:** We performed a retrospective, two-center analysis for patients with ED-SCLC who underwent pretreatment (18)F-FDG PET/CT. Metabolic tumor burden was estimated using whole-body metabolic tumor volume (MTVWB), thoracic metabolic tumor volume (MTVTRX), extra-thoracic metabolic tumor volume (MTVEXT), and the number of extra-thoracic tumor foci. Uni- and multivariate analyses were performed using various clinical factors and the metabolic indices. **RESULTS:** A total of 91 patients were eligible for this study. MTVWB showed stronger correlation with MTVEXT than MTVTRX ($r(2)=0.804$ vs. 0.132 , $p<0.001$, both), whereas no correlation was observed between MTVEXT and MTVTRX ($r(2)=0.007$, $p=0.428$). Patients with smaller MTVWB, MTVEXT, and extra-thoracic tumor foci showed longer survival than patients with larger MTVWB, MTVEXT, and extra-thoracic tumor foci, respectively, whereas the survival difference between patients with smaller MTVTRX and those with larger MTVTRX was not significant. Results of uni- and multivariate analyses showed that ECOG performance status (HR=2.31, $p=0.015$), initial chemotherapy cycles (HR=0.24, $p<0.001$), and the number of extra-thoracic tumor foci (HR=2.75, $p<0.001$) were independent prognostic factors for overall survival, and initial chemotherapy cycles (HR=0.25, $p<0.001$), and MTVEXT (HR=2.04, $p=0.013$) were independent prognostic factors for progression-free survival. **CONCLUSION:** These data provide evidence indicating that extra-thoracic tumor burden but not thoracic tumor burden is an independent prognostic biomarker for ED-SCLC, and support further exploration of novel treatment strategies targeting extra-thoracic tumor burden in order to improve the clinical outcomes of patients with ED-SCLC.

[611]

TÍTULO / TITLE: - Ginsenoside Rg3 induces apoptosis in the U87MG human glioblastoma cell line through the MEK signaling pathway and reactive oxygen species.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 20. doi: 10.3892/or.2013.2555.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2555](#)

AUTORES / AUTHORS: - Choi YJ; Lee HJ; Kang DW; Han IH; Choi BK; Cho WH

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery and Medical Research Institute, Pusan National University Hospital, Busan 602-739, Republic of Korea.

RESUMEN / SUMMARY: - Ginsenoside is known to have potential cancer-preventive activities. The major active components in red ginseng consist of a variety of ginsenosides including Rg3, Rg5 and Rk1, each of which has different pharmacological activities. Among these, Rg3 has been reported to exert anticancer activities through inhibition of angiogenesis and cell proliferation. However, the effects of Rg3 and its molecular mechanism on glioblastoma multiforme (GBM) remain unclear. Therefore, it is essential to develop a greater understanding of this novel compound. In the present study, we investigated the effects of Rg3 on a human glioblastoma cell line and its molecular signaling mechanism. The mechanisms of apoptosis by ginsenoside Rg3 were related with the MEK signaling pathway and reactive oxygen species. Our data suggest that ginsenoside Rg3 is a novel agent for the chemotherapy of GBM.

[612]

TÍTULO / TITLE: - Low-expression of microRNA-107 inhibits cell apoptosis in glioma by upregulation of SALL4.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Jun 28;45(9):1962-1973. doi: 10.1016/j.biocel.2013.06.008.

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

1016/j.biocel.2013.06.008

AUTORES / AUTHORS: - He J; Zhang W; Zhou Q; Zhao T; Song Y; Chai L; Li Y

INSTITUCIÓN / INSTITUTION: - School of Life Science and Technology, Harbin Institute of Technology, Harbin, PR China.

RESUMEN / SUMMARY: - Glioma is the most common highly malignant primary brain tumor. The molecular pathways that result in the pathogenesis of glioma remain elusive. In this study, we found microRNA-107 (miR-107) was downregulated in glioma tissues and cell lines. Our results revealed miR-107 overexpression suppressed cell proliferation in glioma cells, whereas miR-107 knockdown promoted cell growth in MO59K. miR-107 expression induced apoptosis in glioma cells possibly through the increase in Fas (TNFRSF6)-associated via death domain (FADD) expression and activation of caspases-8 and -3/7. Moreover, the activity of caspase-8 in miR-107-overexpressing SHG44 cells was suppressed with FADD knockdown. The tumor growth in nude mice bearing miR-107-overexpressing SHG44 cells was blocked through apoptosis induction. Sal-like 4 (Drosophila) (SALL4) level was reduced upon miR-107 overexpression in glioma cells, and the inverse was observed upon miR-107 knockdown in MO59K. Using a luciferase reporter system, SALL4 3'-UTR-dependent luciferase activity was reduced by miR-107 mimics or increased by an inhibitor of miR-107. In SHG44, SALL4 downregulation

triggered growth inhibition and activated FADD-mediated cell apoptosis pathway. The caspase-8 activity in miR-107-overexpressing SHG44 cells was suppressed with SALL4 upregulation. Furthermore, primary glioma tumors with low miR-107 expression show elevated SALL4 level. An obvious inverse correlation was observed between miR-107 expression and SALL4 level in clinical glioma samples. Therefore, our results demonstrate upregulation of miR-107 suppressed glioma cell growth through direct targeting of SALL4, leading to the activation of FADD/caspase-8/caspase-3/7 signaling pathway of cell apoptosis. These data suggest miR-107 is a potential therapeutic target against glioma.

[613]

TÍTULO / TITLE: - Effect of miR-335 upregulation on the apoptosis and invasion of lung cancer cell A549 and H1299.

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

REVISTA / JOURNAL: - Tumour Biol. 2013 Jun 6.

- Enlace al texto completo (gratis o de pago) [1007/s13277-013-0878-](#)

[9](#)

AUTORES / AUTHORS: - Wang H; Li M; Zhang R; Wang Y; Zang W; Ma Y; Zhao G; Zhang G

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, The First Affiliated Hospital of Zhengzhou University, No.1 Jianshe Road, Zhengzhou, 450052, China.

RESUMEN / SUMMARY: - MicroRNAs are small non-coding RNAs that may also function as oncogenes and tumor-suppressor genes, as the abnormal expression of microRNAs is associated with various human tumors. However, the effect of miR-335 on the lung cancer cells remains unclear. The aim of the paper was to study the expression of miR335 in non-small cell lung cancer (NSCLC) and miR335's relation to the metastasis, invasion, and apoptosis in lung cancer cells A549 and H1299. qRT-PCR was used to identify the miR-335 expression. The effects of miR-335 on cell proliferation, apoptosis, and invasion were further analyzed. Luciferase reporter assay and Western blot were to verify Bcl-w and SP1 as potential major target genes of miR-335. Finally, the effect of Bcl-w on miR-335-induced cell survival was determined. Our results showed that miR-335 expression was significantly lower in NSCLC tissue, which was significantly associated with lymph node metastasis. In contrast to cells in blank and negative control groups, incidence of apoptosis was significantly higher ($P < 0.05$) and the number of cells migrating through matrigel was significantly lower ($P < 0.05$) in miR-335 mimics transfected group. Western blot and luciferase reporter assay demonstrated that miR-335 could bind to the putative binding sites in Bcl-w (or SP1) mRNA 3'-untranslated region to visibly lower the expression of Bcl-w (or SP1). The introduction of Bcl-w cDNA without 3'-untranslated region abrogated miR-335-induced cell survival.

These results indicated that upregulation of miR-335 can simultaneously suppress the invasiveness and promote apoptosis of lung cancer cell A549 and H1299 by targeting Bcl-w and SP1. Therefore, miR-335 may be a potential therapeutic target in NSCLC treatment.

[614]

TÍTULO / TITLE: - There is life in the old dog yet: thymidine kinase as predictive marker in diffuse large B-cell lymphoma.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 16.

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

[3109/10428194.2013.807513](#)

AUTORES / AUTHORS: - Wendtner CM

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Oncology, Immunology, Palliative Care, Infectious Diseases and Tropical Medicine, Klinikum Schwabing, Academic Teaching Hospital of University of Munich, Munich, Germany.

[615]

TÍTULO / TITLE: - The relevance of EGFR overexpression for the prediction of the malignant transformation of oral leukoplakia.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jun 19. doi: 10.3892/or.2013.2545.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2545](#)

AUTORES / AUTHORS: - Ries J; Vairaktaris E; Agaimy A; Bechtold M; Gorecki P; Neukam FW; Nkenke E

INSTITUCIÓN / INSTITUTION: - Department of Oral and Maxillofacial Surgery, Erlangen University Hospital, D-91054 Erlangen, Germany.

RESUMEN / SUMMARY: - The present study evaluated the relevance of EGFR overexpression in prediction of malignant transformation of oral leukoplakia (OLP). The retrospective study comprised paraffin-embedded tissue samples of OLP that transformed into oral squamous cell carcinoma (OSCC) (n=53) and tissue samples of OLP that did not transform into OSCC (n=45) during a follow-up period of 5 years. EGFR overexpression was assessed immunohistochemically. A significantly different expression rate of EGFR was determined between transformed and non-transformed OLP (p=0.017). A statistically significant increase of EGFR expression for low dysplasia lesions in group I compared to group II was proven (D0, p=0.013; D1, p=0.049). By calculation of ROC curve and determination of highest Youden index the optimal threshold value [cut-off point (COP) = 44.96] for distinguishing the transformed from non-transformed lesions was estimated (critical expression rate of EGFR). Using the determined COP the correlation between high-risk

lesions and the detection of increased expression rates were significant ($p=0.001$). In the future, the assessment of EGFR overexpression in OLP may allow identifying OLP lesions with an increased risk of malignant transformation that may have been regarded harmless when only the grade of dysplasia had been taken into account.

[616]

TÍTULO / TITLE: - Anticancer effects of marine carotenoids, fucoxanthin and its deacetylated product, fucoxanthinol, on osteosarcoma.

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

REVISTA / JOURNAL: - Int J Oncol. 2013 Jul 15. doi: 10.3892/ijo.2013.2019.

●● [Enlace al texto completo \(gratis o de pago\) 3892/ijo.2013.2019](#)

AUTORES / AUTHORS: - Rokkaku T; Kimura R; Ishikawa C; Yasumoto T; Senba M; Kanaya F; Mori N

INSTITUCIÓN / INSTITUTION: - Department of Microbiology and Oncology, Graduate School of Medicine, University of the Ryukyus, Nishihara, Okinawa 903-0215, Japan.

RESUMEN / SUMMARY: - Survival of osteosarcoma patients hinges on prevention or treatment of recurrent and metastatic lesions. Therefore, novel chemotherapeutics for more effective treatment and prevention of this disease are required. Carotenoids are natural pigments and exhibit various biological functions. We evaluated the anti-osteosarcoma properties of several carotenoids. Among carotenoids, fucoxanthin and its metabolite fucoxanthinol, inhibited the cell viability of osteosarcoma cell lines. Fucoxanthinol induced G1 cell cycle arrest by reducing the expression of cyclin-dependent kinase 4, cyclin-dependent kinase 6 and cyclin E and apoptosis by reducing the expression of survivin, XIAP, Bcl-2 and Bcl-xL. Apoptosis was associated with activation of caspases-3, -8 and -9. In addition, fucoxanthinol inhibited the phosphorylation of phosphoinositide-dependent kinase 1 and Akt and the downstream glycogen synthase kinase 3 β , resulting in downregulation of beta-catenin. Fucoxanthinol inhibited the cell migration and invasion of osteosarcoma cells. It also reduced matrix metalloproteinase-1 expression and the activator protein-1 signal. Treatment of mice inoculated with osteosarcoma cells with fucoxanthin inhibited the development of osteosarcoma in mice. Fucoxanthin and fucoxanthinol inhibit cell growth, migration and invasion and induce apoptosis of osteosarcoma cells at least in part by inhibiting Akt and activator protein-1 pathways. Our findings provide a rationale for clinical evaluation of these novel agents in osteosarcoma.

[617]

TÍTULO / TITLE: - Predictors of PEG dependence after IMRT+/-chemotherapy for oropharyngeal cancer.

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

REVISTA / JOURNAL: - Radiother Oncol. 2013 Jun 14. pii: S0167-8140(13)00241-7. doi: 10.1016/j.radonc.2013.05.021.

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

[1016/j.radonc.2013.05.021](#)

AUTORES / AUTHORS: - Sanguineti G; Rao N; Gunn B; Ricchetti F; Fiorino C

INSTITUCIÓN / INSTITUTION: - Radiation Oncology, University of Texas Medical Branch, Galveston, USA; Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, USA.

RESUMEN / SUMMARY: - **PURPOSE:** To prospectively assess predictors of PEG dependence after IMRT with/without concomitant chemotherapy (CHT). **METHODS AND MATERIALS:** One-hundred-seventy-one patients were considered (exclusive RT: 58, RT+CHT: 113; 159/171 treated at a median dose of 70Gy, 2Gy/fr). Patients treated with RT+CHT underwent prophylactic PEG insertion; PEG was as needed for the others. A number of clinical factors and dose-volume information concerning oral mucosa (OM), constrictors, masticatory muscles, larynx, esophagus and parotids were available. The 25th/10th percentiles of the duration of PEG dependence were our end-points (respectively 3.3 and 7 months, PEG3/PEG7). Logistic uni and multi-variate (MVA) analyses were performed. **RESULTS:** Concerning PEG3, the independent predictors at MVA were: CHT/PEG policy (OR: 6.8, p=0.001), V9.5G_OMGy/week (OR: 1.017, p=0.01), larynx V50 (OR: 1.018, p=0.01) and superior constrictor (SC) D_mean (OR: 1.002, p=0.005); the predictive value of the model (AUC) was 0.818 (95% CI: 0.751-0.873). The independent predictors of PEG7 were: larynx V50 (OR: 1.042, p=0.0005) and SC D_mean (OR: 1.003, p=0.02), symptoms at diagnosis (yes vs no, OR: 3.6, p=0.08) and sex (male vs female, OR: 0.25, p=0.07); AUC was 0.897 (95% CI: 0.841-0.939). **CONCLUSIONS:** OM V9.5Gy/week and CHT/PEG_policy modulate the risk of early PEG dependence. For longer PEG dependence, larynx V50 (or D_mean) and SC D_mean are highly predictive, suggesting that the fibrosis of constrictors and larynx is the main cause.

[618]

TÍTULO / TITLE: - Impedimetric detection of in situ interaction between anti-cancer drug bleomycin and DNA.

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

REVISTA / JOURNAL: - Int J Biol Macromol. 2013 Jul 26. pii: S0141-8130(13)00408-X. doi: 10.1016/j.ijbiomac.2013.07.012.

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

[1016/j.ijbiomac.2013.07.012](#)

AUTORES / AUTHORS: - Erdem A; Congur G

INSTITUCIÓN / INSTITUTION: - Ege University, Faculty of Pharmacy, Analytical Chemistry Dept., Bornova, 35100 Izmir, Turkey. Electronic address: arzum.erdem@ege.edu.tr.

RESUMEN / SUMMARY: - Surface confined interaction of anti-cancer drug bleomycin (BLM) with nucleic acids: single stranded and double stranded DNA was investigated herein by using electrochemical impedance spectroscopy (EIS) technique in combination with a graphite sensor technology. The experimental conditions were optimized: such as, dsDNA concentration, BLM concentration and interaction time. The main features of impedimetric DNA biosensor, such as its detection limit and the repeatability, were also discussed. The in situ interaction of BLM with dsDNA was also tested impedimetrically in the absence or presence of other chemotherapeutic agents, such as mitomycin C (MC) and cis-platin (cis-DDP) for testing the selectivity.

[619]

TÍTULO / TITLE: - Antitumour effects of Yangzheng Xiaoji in human osteosarcoma: The pivotal role of focal adhesion kinase signalling.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 3. doi: 10.3892/or.2013.2586.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2586](#)

AUTORES / AUTHORS: - Jiang WG; Ye L; Ji K; Ruge F; Wu Y; Gao Y; Ji J; Mason MD

INSTITUCIÓN / INSTITUTION: - Cardiff University-Peking University School of Oncology Joint Institute, Cardiff CF14 4XN, UK.

RESUMEN / SUMMARY: - The present study examined, in vitro and in vivo, the potential antitumour effects of Yangzheng Xiaoji (YZXJ), a traditional Chinese medical formula used in cancer treatment, on osteosarcoma, a tumour type recently found to be sensitive to YZXJ. The human osteosarcoma cell line MG63 was used in cell-matrix adhesion and cell growth assays. The same cell line was used in an in vivo tumour model by establishing subcutaneous osteosarcoma xenografts. Oral and intraperitoneal routes were used to deliver the YZXJ extract. The effect of YZXJ on the activation of focal adhesion kinase (FAK) and paxillin was evaluated by immunofluorescence methods. It was found that YZXJ exhibited a significant inhibitory effect on cell-matrix adhesion as demonstrated by a cell-based assay and electric cell-substrate impedance sensing (ECIS) analysis. The effect was observed together with a reduction in phospho-FAK and phospho-paxillin in the cells when treated with YZXJ. In the in vivo tumour model, YZXJ was found to significantly inhibit the growth of osteosarcoma with a sustained effect observed when YZXJ was delivered intraperitoneally. YZXJ sensitized cells to the effect of FAK inhibitor in vitro and in vivo. It is concluded that Yangzheng Xiaoji plays a significant role in cell-matrix adhesion and tumour growth, likely by inhibiting the activation of the

FAK pathway. The therapeutic role of Yangzheng Xiaoji in osteosarcoma warrants further investigation.

[620]

TÍTULO / TITLE: - Novel Quinolinylaminoisoquinoline Bioisosteres of Sorafenib as Selective RAF1 Kinase Inhibitors: Design, Synthesis, and Antiproliferative Activity against Melanoma Cell Line.

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

REVISTA / JOURNAL: - Chem Pharm Bull (Tokyo). 2013;61(7):747-56.

AUTORES / AUTHORS: - Cho HJ; El-Gamal MI; Oh CH; Lee SH; Sim T; Kim G; Choi HS; Choi JH; Yoo KH

INSTITUCIÓN / INSTITUTION: - Chemical Kinomics Research Center, Korea Institute of Science and Technology.

RESUMEN / SUMMARY: - Design and synthesis of a new series of quinolinylaminoisoquinoline derivatives as conformationally restricted bioisosteres of Sorafenib are described. Their in vitro antiproliferative activity against A375P melanoma cell line was tested. Compounds 1b, 1d, 1g, and 1j showed the highest potency against A375P cell line with IC50 values in sub-micromolar scale. In addition, compound 1d exerted high selectivity towards RAF1 serine/threonine kinase with 96.47% inhibition at 10 microM, and IC50 of 0.96 microM. This compound can possess antiproliferative activity against melanoma cells through inhibition of RAF1 kinase.

[621]

TÍTULO / TITLE: - Oncostatin M promotes mesenchymal stem cell-stimulated tumor growth through a paracrine mechanism involving periostin and TGFBI.

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

REVISTA / JOURNAL: - Int J Biochem Cell Biol. 2013 Aug;45(8):1869-77. doi: 10.1016/j.biocel.2013.05.027. Epub 2013 Jun 2.

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

1016/j.biocel.2013.05.027

AUTORES / AUTHORS: - Lee MJ; Heo SC; Shin SH; Kwon YW; Do EK; Suh DS; Yoon MS; Kim JH

INSTITUCIÓN / INSTITUTION: - Medical Research Center for Ischemic Tissue Regeneration & Medical Research Institute, Yangsan 626-870, Gyeongsangnam-do, Republic of Korea; Department of Physiology, School of Medicine, Pusan National University, Yangsan 626-870, Gyeongsangnam-do, Republic of Korea.

RESUMEN / SUMMARY: - Oncostatin M, a member of the interleukin-6 family of cytokines, has been implicated in tumorigenesis of human prostate cancer. In the current study, we demonstrate that oncostatin M promotes human adipose tissue-derived mesenchymal stem cell-stimulated tumor growth in an in vivo

xenograft transplantation model of the human prostate cancer cell line PC-3M-luc-C6, a PC3M cell line expressing the luciferase gene. Conditioned medium derived from oncostatin M-treated mesenchymal stem cells stimulated adhesion of PC-3M-luc-C6 cells. We identified TGFBI and periostin, extracellular matrix proteins implicated in tumorigenesis and metastasis, as oncostatin M-induced secreted proteins in mesenchymal stem cells. Treatment with oncostatin M stimulated secretion of periostin and TGFBI from mesenchymal stem cells in a time-dependent manner. Immunodepletion of TGFBI and periostin from conditioned medium derived from oncostatin M-treated mesenchymal stem cells resulted in abrogation of adhesion of PC-3M-luc-C6 cells stimulated by oncostatin M-conditioned medium. In addition, small interfering RNA-mediated silencing of TGFBI and periostin resulted in abrogation of cell adhesion stimulated by oncostatin M-conditioned medium. These results suggest that mesenchymal stem cell-derived TGFBI and periostin play a key role in tumorigenesis by stimulating adhesion of prostate cancer cells.

[622]

TÍTULO / TITLE: - MicroRNA-203 down-regulation is associated with unfavorable prognosis in human glioma.

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

REVISTA / JOURNAL: - J Surg Oncol. 2013 Aug;108(2):121-5. doi: 10.1002/jso.23315. Epub 2013 Jun 29.

●● Enlace al texto completo (gratis o de pago) [1002/jso.23315](#)

AUTORES / AUTHORS: - He J; Deng Y; Yang G; Xie W

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Chongqing Red Cross Hospital, Chongqing City, China.

RESUMEN / SUMMARY: - BACKGROUND AND OBJECTIVES: MicroRNA-203 (miR-203) serves as a tumor suppressor or a tumor promoter in different human malignancies. However, its involvement in human gliomas is still unclear. The aim of this study was to investigate the clinical significance of miR-203 expression in gliomas. METHODS: Real-time quantitative PCR was employed to measure the expression level of miR-203 in clinical glioma tissues. RESULTS: The expression of miR-203 was reduced in high WHO grade glioma tissues compared with that in low WHO grade and normal brain tissues, and decreased with ascending tumor WHO grades ($P < 0.001$). The reduced miR-203 expression in gliomas was significantly associated with higher WHO grade ($P < 0.001$), lower KPS score ($P = 0.008$) and poorer disease-specific survival of patients ($P = 0.001$). More importantly, subgroup analyses according to tumor WHO grade revealed that the disease-specific survival of patients with low miR-203 expression in high WHO grades (III-IV) subgroup was significantly shorter than those with high miR-203 expression ($P < 0.001$), but no significant difference was found for patients in WHO grades I-II subgroup ($P = 0.08$). CONCLUSION: Our data validate an important clinical significance of miR-203

in gliomas, and reveal that it might be an intrinsic regulator of tumor progression and a potential prognostic factor for this dismal disease. *J. Surg. Oncol.* 2013; 108:121-125. © 2013 Wiley Periodicals, Inc.

[623]

TÍTULO / TITLE: - The influence of R substituents in triphenylphosphinegold(I) carbonimidothioates, PhPAu[SC(OR)=NPh] (R=Me, Et and iPr), upon in vitro cytotoxicity against the HT-29 colon cancer cell line and upon apoptotic pathways.

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

REVISTA / JOURNAL: - *J Inorg Biochem.* 2013 May 28;127C:24-38. doi: 10.1016/j.jinorgbio.2013.05.011.

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

1016/j.jinorgbio.2013.05.011

AUTORES / AUTHORS: - Yeo CI; Ooi KK; Akim AM; Ang KP; Fairuz ZA; Halim SN; Ng SW; Seng HL; Tiekink ER

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia.

RESUMEN / SUMMARY: - The Ph₃PAu[SC(OR)=NPh], R=Me (1), Et (2) and iPr (3), compounds are significantly cytotoxic to the HT-29 cancer cell line with 1 being the most active. Based on human apoptosis PCR-array analysis, caspase activities, DNA fragmentation, cell apoptotic assays, intracellular reactive oxygen species (ROS) measurements and human topoisomerase I inhibition, induction of apoptosis is demonstrated and both the extrinsic and intrinsic pathways of apoptosis have been shown to occur. Compound 1 activates the p73 gene, whereas each of 2 and 3 activates the p53 gene. An additional apoptotic mechanism is exhibited by 2, that is, via the JNK/MAP pathway.

[624]

TÍTULO / TITLE: - The issue of studies evaluating biomarkers which predict outcome after pemetrexed-based chemotherapy in malignant pleural mesothelioma.

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

REVISTA / JOURNAL: - *J Thorac Oncol.* 2013 Aug;8(8):e80-2. doi: 10.1097/JTO.0b013e31829b1cf9.

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

1097/JTO.0b013e31829b1cf9

AUTORES / AUTHORS: - Mairinger F; Vollbrecht C; Mairinger T; Popper H

INSTITUCIÓN / INSTITUTION: - Institute of Pathology and Neuropathology University Hospital Essen University of Duisburg-Essen Essen, Germany Institute of Pathology University Hospital Cologne Cologne, Germany Institute

of Pathology Helios Klinikum Emil von Behring Berlin, Germany Institute of Pathology Medical University Graz, Graz, Austria.

[625]

TÍTULO / TITLE: - Andrographolide causes apoptosis via inactivation of STAT3 and Akt and potentiates antitumor activity of gemcitabine in pancreatic cancer.

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

REVISTA / JOURNAL: - Toxicol Lett. 2013 Jul 8;222(1):23-35. doi: 10.1016/j.toxlet.2013.06.241.

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

[1016/j.toxlet.2013.06.241](#)

AUTORES / AUTHORS: - Bao GQ; Shen BY; Pan CP; Zhang YJ; Shi MM; Peng CH

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of medicine (SJTU-SM), Shanghai 200025, PR China.

RESUMEN / SUMMARY: - Gemcitabine is a first-line drug utilised in the chemotherapy of pancreatic cancer; however, this drug induces chemoresistance and toxicity to normal tissue during treatment. Here, we firstly report that andrographolide (ANDRO) alone not only has anti-pancreatic cancer activity, but it also potentiates the anti-tumour activity of gemcitabine. Treatment with ANDRO alone inhibits proliferation of the pancreatic cancer cell lines in a dose- and time-dependent manner in vitro. Interestingly, ANDRO induces cell cycle arrest and apoptosis of pancreatic cancer cells by inhibiting STAT3 and Akt activation, upregulating the expression of p21WAF1 and Bax, and downregulating the expression of cyclinD1, cyclinE, survivin, X-IAP and Bcl-2. Additionally, ANDRO combined with gemcitabine significantly induce stronger cell cycle arrest and more obvious apoptosis than each single treatment. The mechanistic study demonstrates that this synergistic effect is also dependent on the inhibition of STAT3 and Akt activations which subsequently regulates the pathways involved in the apoptosis and cell cycle arrest. Furthermore, both ANDRO alone and the combination treatments exhibit efficacious anti-tumour activity in vivo. Overall, our results provide solid evidence supporting that ANDRO alone or its combination with gemcitabine is a potential chemotherapeutic approach for treating human pancreatic cancer in clinical practice.

[626]

TÍTULO / TITLE: - Copper(II) mixed chelate compounds induce apoptosis through reactive oxygen species in neuroblastoma cell line CHP-212.

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

REVISTA / JOURNAL: - J Inorg Biochem. 2013 Sep;126:17-25. doi: 10.1016/j.jinorgbio.2013.05.001. Epub 2013 May 7.

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

[1016/j.jinorgbio.2013.05.001](http://dx.doi.org/10.1016/j.jinorgbio.2013.05.001)

AUTORES / AUTHORS: - Gutierrez AG; Vazquez-Aguirre A; Garcia-Ramos JC; Flores-Alamo M; Hernandez-Lemus E; Ruiz-Azuara L; Mejia C

INSTITUCIÓN / INSTITUTION: - Departamento de Medicina Genomica y Toxicologia Ambiental, Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico, Mexico D.F., Mexico.

RESUMEN / SUMMARY: - In the present work we report the antiproliferative activity of Cu(II) coordination compounds, CasIIgly ([Cu(4,7-dimethyl-1,10-phenanthroline) (glycinato) (H₂O)]NO₃), CasIIIa ([Cu(4,4'-dimethyl-2,2'-bipyridine) (glycinato) (H₂O)]NO₃), and CasIIIEa ([Cu(4,7-dimethyl-1,10-phenanthroline) (acetylacetonato) (H₂O)]NO₃), against human tumoral cell line CHP-212 (stromal neuroblastoma). Additionally, the molecular structure of CasIIIEa was reported. The IC₅₀ values obtained for the evaluated compounds are in the range 18 to 47 μM, representing an inhibition potency increase of 5 to 12 times compared with cisplatin (IC₅₀=226.7 μM). After 2h of incubation with the evaluated compounds, cells showed high levels of reactive oxygen species and a considerable GSH depletion, besides an important disruption of the mitochondrial membrane with release of cytochrome C and besides the presence of caspase-3, an effector caspase that is activated in the last step of apoptosis cascade. The results confirm that cell death in neuroblastoma CHP-212 treated with Casiopeinas occurs via apoptosis. Due to the lack of expression of caspase-8, cell death is principally by the mitochondrial pathway. Thus, one of the most interesting findings of this work is the identification of a very important damage in neuroblastoma cells induced by Cu(II) coordination compounds in a very short exposition times.

[627]

TÍTULO / TITLE: - Cetuximab promotes anticancer drug toxicity in rhabdomyosarcomas with EGFR amplification in vitro.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 4. doi: 10.3892/or.2013.2588.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2588](http://dx.doi.org/10.3892/or.2013.2588)

AUTORES / AUTHORS: - Yamamoto Y; Fukuda K; Fuchimoto Y; Matsuzaki Y; Saikawa Y; Kitagawa Y; Morikawa Y; Kuroda T

INSTITUCIÓN / INSTITUTION: - Department of Pediatric Surgery, Keio University School of Medicine, Tokyo 160-858, Japan.

RESUMEN / SUMMARY: - Overexpression of human epidermal growth factor receptor (EGFR) has been detected in various tumors and is associated with poor outcomes. Combination treatment regimens with EGFR-targeting and cytotoxic agents are a potential therapeutic option for rhabdomyosarcoma

(RMS) with EGFR amplification. We investigated the effects of combination treatment with actinomycin D and the EGFR-targeting agent cetuximab in 4 RMS cell lines. All 4 RMS cell lines expressed wild-type K-ras, and 2 of the 4 overexpressed EGFR, as determined by flow cytometry, real-time PCR and direct sequencing. Combination of cetuximab and actinomycin D was highly effective, synergistically inhibiting cell growth with a combination index of less than 1. Moreover, combination treatment with these two reagents increased the rate of apoptosis in EGFR-positive cells. Cetuximab has antitumor activity in EGFR-amplified RMS cells when combined with antitumor reagents, indicating that cetuximab is a potential therapeutic reagent for RMS with EGFR amplification.

[628]

TÍTULO / TITLE: - Bladder preservation therapy for muscle-invading bladder cancers on radiation therapy oncology group trials 8802, 8903, 9506, and 9706: vascular endothelial growth factor B overexpression predicts for increased distant metastasis and shorter survival.

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

REVISTA / JOURNAL: - Oncologist. 2013;18(6):685-6. doi: 10.1634/theoncologist.2012-0461. Epub 2013 May 31.

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

[1634/theoncologist.2012-0461](#)

AUTORES / AUTHORS: - Lautenschlaeger T; George A; Klimowicz AC; Efstathiou JA; Wu CL; Sandler H; Shipley WU; Tester WJ; Hagan MP; Magliocco AM; Chakravarti A

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Wexner Medical Center, Ohio State University, Columbus, Ohio, USA;

RESUMEN / SUMMARY: - From 1988 to 1999, the Radiation Therapy Oncology Group (RTOG) conducted four prospective studies (8802, 8903, 9506, 9706) of patients with clinical stage T2-4^a muscle-invasive bladder cancer. Treatment was selective bladder preservation using transurethral surgery (TURBT) plus cisplatin-based induction and consolidation chemoradiation regimens, reserving radical cystectomy for invasive tumor recurrence. We investigated vascular endothelial growth factor (VEGF) pathway biomarkers in this unique clinical dataset (median follow-up of 3.1 years). Methods. A total of 43 patients with tissue available from the entry TURBT were included in this analysis. Expression of VEGF ligands and receptors were quantified and scored by the AQUA platform (HistoRX, now Genoptix, Carlsbad, CA) and analyzed after median split. Results. VEGF expression levels were not associated with increased rates of complete response to induction chemoradiation. Higher levels of cytoplasmic VEGF-B, VEGF-C, and VEGF-R2 were associated with decreased overall survival rates. The 3-year overall survival estimates for high and low expressers were 43.7% and 75% for VEGF-B cytoplasm ($p = .01$),

40.2% and 86.7% for VEGF-C cytoplasm ($p = .01$), and 49.7% and 66.7% for VEGF-R2 cytoplasm ($p = .02$). Higher expression levels of cytoplasm VEGF-B were associated with higher rates of distant failure ($p = .01$). Conclusions. Although VEGF ligands and receptors do not appear to be associated with complete response to induction chemoradiation for muscle-invasive bladder cancer, we report significant associations with overall survival and distant failure for certain VEGF family members.

[629]

TÍTULO / TITLE: - Mechanisms of Drug Resistance in Cancer Chemotherapy: Coordinated Role and Regulation of Efflux Transporters and Metabolizing Enzymes.

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

REVISTA / JOURNAL: - Curr Pharm Des. 2013 Jul 3.

AUTORES / AUTHORS: - Vadlapatla RK; Vadlapudi AD; Pal D; Mitra AK

INSTITUCIÓN / INSTITUTION: - Department of Pharmaceutical Sciences, School of Pharmacy, University of Missouri - Kansas City, 2464 Charlotte Street, Kansas City MO 64108-2718 USA.

RESUMEN / SUMMARY: - Cancer remains one of the major leading causes of death worldwide. Acquisition of multidrug resistance (MDR) remains a major impediment to successful chemotherapy. As the name implies, MDR is not limited only to one drug but often associated to structurally and functionally unrelated chemotherapeutics. Extensive research and investigations have identified several mechanisms underlying the development of MDR. This process of drug resistance is considered to be multifactorial including decreased drug accumulation, increased efflux, increased biotransformation, drug compartmentalization, modification of drug targets and defects in cellular pathways. In the first part of the review, these pharmacokinetic and pharmacodynamic mechanisms have been described in brief. Although the pathways can act independently, they are more often intertwined. Of the various mechanisms involved, up-regulation of efflux transporters and metabolizing enzymes constitute a major resistance phenotype. This review also provides a general biological overview of important efflux transporters and metabolizing enzymes involved in MDR. Further, synergistic action between efflux transporters and metabolizing enzymes leading to MDR could possibly arise due to two different factors; overlapping substrate specificity and coordinated regulation of their expression. The expression of efflux transporters and metabolizing enzymes is governed by nuclear receptors, mainly pregnane X receptor (PXR). The pharmacological role of PXR and advances in the development of PXR antagonists to overcome MDR are outlined.

[630]

TÍTULO / TITLE: - The tricyclic antidepressant amitriptyline is cytotoxic to HTB114 human leiomyosarcoma and induces p75NTR-dependent apoptosis.

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

REVISTA / JOURNAL: - Anticancer Drugs. 2013 Jul 18.

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

[1097/CAD.0b013e328364312f](#)

AUTORES / AUTHORS: - Pula G; Pistilli A; Montagnoli C; Stabile AM; Rambotti MG; Rende M

INSTITUCIÓN / INSTITUTION: - Anatomy Section, Department of Medico-Surgical Specialties and Public Health, School of Medicine, University of Perugia, Perugia, Italy.

RESUMEN / SUMMARY: - Nerve growth factor (NGF) receptors, TrKA and p75, are being investigated in cancer therapy. Our previous data show that, in HTB114 uterine leiomyosarcoma cells, p75-dependent apoptosis is inducible by cytotoxic drugs and can suppress nerve growth factor-dependent growth. Although amitriptyline can kill cancer cells and bind TrKA/B, its effects on p75-dependent apoptosis are unknown. The aim of this paper was to evaluate the antineoplastic potential of amitriptyline, and the role of p75-dependent apoptosis in the chemoresistant uterine HTB114 leiomyosarcoma. Using proliferation assays and fluorescence-activated cell sorting analysis, we found that amitriptyline caused a marked reduction in HTB114 cell viability, associated with the parallel upregulation of p75 expression. This converted the TrKA-proliferating cells into TrKA/p75, leading to downregulation of TrKA-prosurvival signaling (AKT) and activation of p75-dependent apoptosis (through caspase-3). Overall, we provide novel evidence that HTB114 uterine leiomyosarcoma cells are highly sensitive to amitriptyline, supporting the role of p75-dependent apoptosis as a novel cytotoxic mechanism of this drug and of p75 as an inducible stress receptor and a novel target in clinical oncology.

[631]

TÍTULO / TITLE: - Zidovudine-Based Lytic-Inducing Chemotherapy for Epstein-Barr Virus-Related Lymphomas.

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

REVISTA / JOURNAL: - Leuk Lymphoma. 2013 Jul 10.

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

[3109/10428194.2013.818142](#)

AUTORES / AUTHORS: - Bayraktar UD; Diaz LA; Ashlock B; Toomey N; Cabral L; Bayraktar S; Pereira D; Dittmer DP; Ramos JC

RESUMEN / SUMMARY: - ABSTRACT Treatment of Epstein Barr virus (EBV)-related lymphomas with lytic-inducing agents is an attractive targeted approach for eliminating virus infected tumor cells. Zidovudine (AZT) is an excellent substrate for EBV-thymidine kinase; can induce EBV lytic gene expression and apoptosis in primary EBV+ lymphoma cell lines. We hypothesized that the

combination of AZT with lytic-inducing chemotherapy agents would be effective in treating EBV+ lymphomas. We report a retrospective analysis of 19 patients with aggressive EBV+ non-Hodgkin's lymphoma, including 9 cases of AIDS-associated primary central nervous system lymphoma (AIDS-PCNSL) treated with AZT-based chemotherapy. Our results demonstrate that high-dose AZT-methotrexate is efficacious in treating highly aggressive systemic EBV+ lymphomas in the upfront setting. In primary EBV+ lymphoma cell lines, the combination of AZT with hydroxyurea resulted in synergistic EBV lytic induction and cell death. Further, AZT-hydroxyurea treatment resulted in dramatic responses in patients with AIDS-PCNSL. The combination of AZT with chemotherapy, especially lytic-inducing agents, should be explored further in clinical trials for the treatment of EBV-related lymphomas.

[632]

TÍTULO / TITLE: - 4-Hydroxybenzyl alcohol: A novel inhibitor of tumor angiogenesis and growth.

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

REVISTA / JOURNAL: - Life Sci. 2013 Jul 19;93(1):44-50. doi: 10.1016/j.lfs.2013.05.022. Epub 2013 Jun 3.

●● Enlace al texto completo (gratis o de pago) 1016/j.lfs.2013.05.022

AUTORES / AUTHORS: - Laschke MW; Vorsterman van Oijen AE; Korbel C; Scheuer C; Menger MD

INSTITUCIÓN / INSTITUTION: - Institute for Clinical & Experimental Surgery, University of Saarland, 66421 Homburg/Saar, Germany. Electronic address: matthias.laschke@uks.eu.

RESUMEN / SUMMARY: - AIMS: The herbal compound 4-hydroxybenzyl alcohol (HBA) is a pleiotropic agent, which has been shown to effectively inhibit the development of new blood vessels by targeting multiple mechanisms of the angiogenic process. Because angiogenesis is a major prerequisite for tumor growth, the aim of this study was to analyze for the first time, whether HBA may be used for anti-cancer therapy. MAIN METHODS: CT26.WT colon carcinoma cells were exposed to different HBA doses to study their viability, migration, invasiveness and protein expression compared to vehicle-treated controls. Moreover, CT26.WT cell spheroids were transplanted into the dorsal skinfold chamber of HBA-treated and vehicle-treated BALB/c mice for the analysis of tumor vascularization and growth by means of repetitive intravital fluorescence microscopy, histology and immunohistochemistry. KEY FINDINGS: As shown by water-soluble tetrazolium (WST)-1 and lactate dehydrogenase (LDH) assays, HBA treatment dose-dependently reduced the viability and integrity of the tumor cells. Moreover, phalloidin staining of HBA-treated cells revealed a disorganized cytoskeleton, which was associated with a decreased cellular migratory and invasive activity. In addition, the cells presented with a significantly increased expression of the apoptosis marker cleaved caspase-3

and a decreased expression of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 when compared to controls. Finally, HBA treatment inhibited the vascularization and growth of newly developing CT26.WT tumors in the mouse dorsal skinfold chamber model without affecting the normal behavior of the animals. SIGNIFICANCE: These novel findings indicate that HBA represents a promising candidate for the establishment of anti-angiogenic treatment strategies in cancer therapy.

[633]

TÍTULO / TITLE: - The case for aromatase inhibitors use in Oncofertility patients. Should aromatase inhibitors be combined with gonadotropin treatment in Breast Cancer patients undergoing ovarian stimulation for fertility preservation prior to chemotherapy? A debate.

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

REVISTA / JOURNAL: - Hum Fertil (Camb). 2013 Jul 17.

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

[3109/14647273.2013.800650](#)

AUTORES / AUTHORS: - Fatum M; McVeigh E; Child T

INSTITUCIÓN / INSTITUTION: - Oxford Fertility Unit, Institute of Reproductive Sciences, Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK.

RESUMEN / SUMMARY: - Breast cancer is one of the hormone-dependent cancers that may be adversely affected by elevated oestrogen or progesterone concentrations, particularly the endocrine active (hormone receptor positive) breast cancers. Treatment for breast cancer patients aimed at fertility preservation, includes ovarian hyperstimulation, the harvest of oocytes, and subsequent cryopreservation of oocytes or embryos. Classically, gonadotrophins have been used effectively for ovulation induction, a treatment often accompanied by high blood oestrogen concentrations produced by the hyperstimulated granulosa cells. Despite the uncertainty which surrounds this issue and the lack of clear-cut clinical evidence, it is still of major concern that these ensuing high hormone levels might be associated with a high risk of recurrence of the cancer. A growing number of clinical studies have strongly suggested the benefits of using aromatase inhibitors in infertility treatment, both as single agents or as adjuncts to FSH-containing ovulation induction regimes in reproductive medicine. Combining gonadotrophins with aromatase inhibitors would augment the stimulation effect, with a reduced increase in serum concentrations of estradiol. We propose to open a debate over the use of aromatase inhibitors in combination with FSH in ovulation induction treatment of breast cancer oncofertility patients. As the safety of aromatase inhibitors such as letrozole has recently been demonstrated in several studies, and there is growing concern over the possible detrimental effects of high estradiol levels on breast cancer cells (at least in mouse models), the co-administration of letrozole

in these patients would reduce both the high supraphysiologic serum levels of estradiol and the intratumoral in situ production of oestrogen. However, since it is unlikely that a well-founded evidence-based justification of this treatment will be formulated in the near future, based on well-designed prospective randomised controlled trials, we advocate a wider use of aromatase inhibitors in combination with gonadotrophins in breast cancer patients, especially those with hormone-receptor-positive tumours.

[634]

TÍTULO / TITLE: - Perturbation of proteasome function by bortezomib leading to ER stress-induced apoptotic cell death in cholangiocarcinoma.

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

REVISTA / JOURNAL: - J Cancer Res Clin Oncol. 2013 Jul 23.

- [Enlace al texto completo \(gratis o de pago\) 1007/s00432-013-1473-](#)

[6](#)

AUTORES / AUTHORS: - Vaeteewoottacharn K; Kariya R; Matsuda K; Taura M; Wongkham C; Wongkham S; Okada S

INSTITUCIÓN / INSTITUTION: - Division of Hematopoiesis, Center for AIDS Research, Kumamoto University, 2-2-1 Honjo, Kumamoto, 860-0811, Japan.

RESUMEN / SUMMARY: - PURPOSE: Cholangiocarcinoma (CCA) or cancer of the biliary tract is heterogeneous; however, chronic inflammatory-related features are unique in CCA. Moreover, the genes involved in proteasome functions are evidently increased in CCA. Hence, CCA might be vulnerable to endoplasmic reticulum (ER) stressors, particularly a proteasome inhibitor. Therefore, bortezomib (BTZ), a specific 26S proteasome inhibitor, was selected, and its antitumor effects against CCA were investigated. METHODS: Liver fluke-associated CCA cell lines were used. Cell proliferation and apoptosis detection were determined by a tetrazolium-based assay, caspase detection and annexin V binding assay. The accumulations of proteasome substrates, the inductions of ER stress and unfolded protein response (UPR) proteins were demonstrated by western blot and reporter systems. The in vivo anti-proliferative effect was accessed in a subcutaneous transplantation mouse model. RESULTS: BTZ inhibited CCA proliferation and induced caspase-dependent apoptosis, independently of the NF-kappaB pathway. Inhibition of protein degradation by BTZ led to the induction of UPR; induction of XBP1 splicing, ATF6 proteolysis and nuclear ATF4 as well as BiP and CHOP expressions were evident. Nevertheless, ER stress-induced UPR was overwhelming, leading to the activation of apoptosis demonstrated by proteolytic cleavages of ER-related caspase 4 and 12 as well as classical caspase 8, 9 and 3. The growth inhibitory effect of BTZ was supported by an in vivo model. CONCLUSION: BTZ treatment could be a promising therapeutic approach for CCA treatment.

[635]

TÍTULO / TITLE: - IC-4, a new irreversible EGFR inhibitor, exhibits prominent anti-tumor and anti-angiogenesis activities.

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

REVISTA / JOURNAL: - Cancer Lett. 2013 Jul 12. pii: S0304-3835(13)00510-7. doi: 10.1016/j.canlet.2013.07.005.

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

[1016/j.canlet.2013.07.005](#)

AUTORES / AUTHORS: - Li YB; Wang ZQ; Yan X; Chen MW; Bao JL; Wu GS; Ge ZM; Zhou DM; Wang YT; Li RT

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China.

RESUMEN / SUMMARY: - Accumulating evidence suggested that the irreversible tyrosine kinase inhibitors (TKIs) have potential to override the acquired resistance to target-based therapies. Herein, we reported IC-4 as a novel irreversible TKI for epidermal growth factor receptor (EGFR). IC-4 potentially suppressed proliferation, induced apoptosis and a G2/M cell cycle arrest in breast cancer cells, correlating with inhibition of EGF-induced EGFR activation, but independent of DNA damage. In addition, IC-4 exhibited anti-angiogenic activities both in vitro and in vivo. It suppressed cell viability and proliferation induced by various growth factors in human umbilical vein endothelial cells (HUVECs). IC-4 also inhibited HUVECs migration and tube formation. In transgenic zebrafish embryo model, IC-4 was shown to suppress formation of intersegmental vessel and development of subintestinal vessels. Taken together, these results demonstrated that IC-4 is a new irreversible EGFR-TKI, exhibiting potent anti-breast cancer and anti-angiogenic effects.

[636]

TÍTULO / TITLE: - MicroRNA-375 sensitizes tumour necrosis factor-alpha (TNF-alpha)-induced apoptosis in head and neck squamous cell carcinoma in vitro.

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

REVISTA / JOURNAL: - Int J Oral Maxillofac Surg. 2013 Aug;42(8):949-55. doi: 10.1016/j.ijom.2013.04.016. Epub 2013 May 29.

●● Enlace al texto completo (gratis o de pago) [1016/j.ijom.2013.04.016](#)

AUTORES / AUTHORS: - Wang J; Huang H; Wang C; Liu X; Hu F; Liu M

INSTITUCIÓN / INSTITUTION: - Department of Oral and Maxillofacial Surgery, Guanghua School of Stomatology, Institute of Stomatological Research, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Stomatology, Guangzhou, China.

RESUMEN / SUMMARY: - We investigated the effect of microRNA-375 (miR-375) on tumour necrosis factor-alpha (TNF-alpha)-induced cell death in head and

neck squamous cell carcinoma, and further explored the potential molecular mechanism underlying this phenomenon. Cal27 cells were transfected with miR-375 mimic and subsequently treated with or without TNF-alpha (10ng/ml). An additional group of cells were treated with TNF-alpha alone. The resulting morphological changes were observed, and the percentage of sub-G1 cells was measured. The protein expression and cleavage of caspase 3, caspase 8, and poly(ADP ribose) polymerase (PARP) were determined through Western blotting. The results showed a significant increase in cell death in the combination group, but not in the groups treated with miR-375 mimic, TNF-alpha alone, or control. The data obtained from sub-G1 cells supported the notion that miR-375 increases the accumulation of sub-G1. In the combination group, the degradation of caspase 3, caspase 8, and PARP was observed and the cleavage of these enzymes was detected. The pan-caspase inhibitor, Z-VAD, inhibited the apoptosis of Cal27 cells treated with a combination of miR-375 mimic and TNF-alpha. In addition, the apoptosis inhibitory proteins, cFLIP-L and cIAP1, were down-regulated in a time-dependent manner. Taken together, these data suggest that miR-375 sensitizes TNF-alpha-induced apoptosis, and the reduction in the expression of the apoptosis inhibitory proteins cFLIP-L and cIAP2 plays an important role in this sensitization.

[637]

TÍTULO / TITLE: - Kruppel-like factor 8 overexpression is correlated with angiogenesis and poor prognosis in gastric cancer.

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

REVISTA / JOURNAL: - World J Gastroenterol. 2013 Jul 21;19(27):4309-15. doi: 10.3748/wjg.v19.i27.4309.

●● Enlace al texto completo (gratis o de pago) [3748/wjg.v19.i27.4309](#)

AUTORES / AUTHORS: - Wang WF; Li J; Du LT; Wang LL; Yang YM; Liu YM; Liu H; Zhang X; Dong ZG; Zheng GX; Wang CX

INSTITUCIÓN / INSTITUTION: - Wen-Fei Wang, School of Biosciences, University of Nottingham, Sutton Bonington Campus, Loughborough, Leics, LE12 5RD, United Kingdom.

RESUMEN / SUMMARY: - AIM: To investigate Kruppel-like factor 8 (KLF8) expression in gastric cancer and its relationship with angiogenesis and prognosis of gastric cancer. METHODS: One hundred and fifty-four patients with gastric cancer who underwent successful curative resection were retrospectively enrolled in the study. Fifty tumor-adjacent healthy gastric tissues (>= 5 cm from the tumor margin) obtained during the original resection were randomly selected for comparative analysis. In situ expression of KLF8 and CD34 proteins were examined by immunohistochemistry. The intratumoral microvessel density (MVD) was determined by manually counting the immunostained CD34-positive endothelial cells in three consecutive high-magnification fields (x 200). The relationship between differential KLF8

expression and MVD was assessed using Spearman's correlation coefficient test. chi(2) test was performed to evaluate the effects of differential KLF8 expression on clinicopathologic factors. Kaplan-Meier and multivariate Cox survival analyses were used to assess the prognostic value of differential KLF8 expression in gastric cancer. RESULTS: Significantly higher levels of KLF8 protein were detected in gastric cancer tissues than in the adjacent non-cancerous tissues (54.5% vs 34.0%, $P < 0.05$). KLF8 expression was associated with tumor size ($P < 0.001$), local invasion ($P = 0.005$), regional lymph node metastasis ($P = 0.029$), distant metastasis ($P = 0.023$), and tumor node metastasis (TNM) stage ($P = 0.002$), as well as the MVD ($r = 0.392$, $P < 0.001$). Patients with KLF8 positive expression had poorer overall survival ($P < 0.001$) and cancer-specific survival ($P < 0.001$) than those with negative expression. Multivariate analysis demonstrated that KLF8 expression independently affected both overall and cancer-specific survival of gastric cancer patients ($P = 0.035$ and 0.042 , respectively). CONCLUSION: KLF8 is closely associated with gastric tumor progression, angiogenesis and poor prognosis, suggesting it may represent a novel prognostic biomarker and therapeutic target for gastric cancer.

[638]

TÍTULO / TITLE: - Aristolochia debilis Sieb. et Zucc. Induces Apoptosis and Reactive Oxygen Species in the HT-29 Human Colon Cancer Cell Line.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1089/cbr.2013.1486](#)

AUTORES / AUTHORS: - Li C; Wang MH

INSTITUCIÓN / INSTITUTION: - Department of Medical Biotechnology, Kangwon National University, Chuncheon-Si, South Korea .

RESUMEN / SUMMARY: - Abstract In this study, we investigated the potential anticancer effect and mechanisms of action of a methanol extract from Aristolochia debilis Sieb. et Zucc (A. debilis) stems on human colon cancer cells (HT-29). A. debilis inhibited proliferation of HT-29 cells in dose-dependent and time-dependent manners as detected by the 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan assay. A cell cycle analysis was performed via propidium iodide staining and flow cytometry. The A. debilis extract affected cell cycle progression by inducing sub-G1 arrest. The reactive oxygen species (ROS) level was determined by dichlorofluorescein diacetate. A decrease in the mitochondrial membrane potential and inhibition of manganese superoxide dismutase in combination with the accumulation of ROS induced apoptosis. Reverse transcription-polymerase chain reaction and Western blot analyses were used to determine changes in the expression of mitochondria-dependent apoptosis markers (Bax and Bcl-2). Upregulation of Bax and corresponding

downregulation of Bcl-2 expression as well as ROS production may be the critical mechanism through which *A. debilis* induced apoptosis in HT-29 cells.

[639]

TÍTULO / TITLE: - FAM9C plays an anti-apoptotic role through activation of the PI3K/Akt pathway in human hepatocellular carcinoma.

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

REVISTA / JOURNAL: - Oncol Rep. 2013 Jul 5. doi: 10.3892/or.2013.2592.

●● Enlace al texto completo (gratis o de pago) [3892/or.2013.2592](#)

AUTORES / AUTHORS: - Zhou JD; Shen F; Ji JS; Zheng K; Huang M; Wu JC

INSTITUCIÓN / INSTITUTION: - The Core Laboratory of the Suzhou Cancer Center and Department of Radiotherapy of the Suzhou Hospital Affiliated to Nanjing Medical University, Suzhou 215001, P.R. China.

RESUMEN / SUMMARY: - The function of FAM9C encoding a testis-exclusively expressed and nuclear-localized protein remains unknown. In the present study, we evaluated the role of FAM9C in human hepatocellular carcinoma. We found that among three FAM9 family members, only FAM9C was frequently upregulated in HCC specimens compared with that in corresponding adjacent non-cancer liver tissues. FAM9C was located in the nucleus of HCC cells, as shown by both western blotting and immunofluorescence assays. Significantly, FAM9C overexpression promoted proliferation, clonogenicity in an anchorage-dependent manner, in vivo tumorigenicity of YY-8103, and Huh-7 cells. In contrast, FAM9C knockdown suppressed proliferation, anchorage-dependent colony formation and in vivo tumorigenicity of QGY-7703, and BEL-7404 cells. However, FAM9C had no significant effects on cell cycle progression when FAM9C was stably overexpressed in Huh-7 cells or knocked down in BEL-7404 cells. Most importantly, FAM9C regulated activation of Akt and UV-induced apoptosis in HCC cells. FAM9C overexpression increased the phosphorylation levels of Akt and anti-apoptotic ability of Huh-7 cells, whereas endogenous FAM9C knockdown reduced the phosphorylated levels of Akt and anti-apoptotic ability of BEL-7404 cells. Furthermore, the anti-apoptotic function of FAM9C could be prevented when the PI3K-Akt pathway was in a loss-of-function caused by RNA interference against Akt or PI3K inhibitor LY294002 in HCC cells. Taken together, our data demonstrate that FAM9C as a novel cancer testis gene plays an anti-apoptotic role in human hepatocellular carcinoma through activating the PI3K/Akt signaling pathway, and serves as a promising target for HCC therapy.

[640]

TÍTULO / TITLE: - Targeting renal cancer with a combination of WNT inhibitors and a bi-functional peptide.

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

REVISTA / JOURNAL: - Anticancer Res. 2013 Jun;33(6):2435-40.

AUTORES / AUTHORS: - Koller CM; Kim Y; Schmidt-Wolf IG

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine III, Center for Integrated Oncology, University Hospital Bonn, 53105 Bonn, Germany.

Ingo.Schmidt-Wolf@ukb.uni-bonn.de

RESUMEN / SUMMARY: - AIM: Advanced renal cancer has still a very poor prognosis. We combined wingless-related integration site (WNT) inhibitors with a bi-functional peptide, as previous research has proven their individual efficacy in cancer therapy. Each targets cancer cells differently. We wanted to determine whether they have an additive effect. MATERIALS AND METHODS: Our bi-functional peptide consists of a target domain (LTVSPWY) and a lytic domain (KLAKLAK)2. We used three WNT inhibitors: Ethacrinic acid, ciclopirox olamine, piroctone olamine and combined each with the bi-functional peptide. They were tested on three different renal cancer cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium-bromide (MTT) assay. RESULTS: We demonstrated a synergistic effect of WNT inhibitors with the bi-functional peptide. The vitality of cancer cells was reduced significantly ($p < 0.05$), while healthy cells were mostly unaffected. CONCLUSION: The combination of WNT inhibitor and the bi-functional peptide may lead to new treatment options as toxic side-effects can be reduced due to the lower doses of agent required.

[641]

TÍTULO / TITLE: - Mechanisms of proteasome inhibitor-induced cytotoxicity in malignant glioma.

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

REVISTA / JOURNAL: - Cell Biol Toxicol. 2013 Jun 5.

●● [Enlace al texto completo \(gratis o de pago\) 1007/s10565-013-9248-](#)

[Z](#)

AUTORES / AUTHORS: - Vlachostergios PJ; Voutsadakis IA; Papandreou CN

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Faculty of Medicine, University of Thessaly, University Hospital of Larissa, Larissa, 41110, Greece, pvlacho@med.uth.gr.

RESUMEN / SUMMARY: - The 26S proteasome constitutes an essential degradation apparatus involved in the consistent recycling of misfolded and damaged proteins inside cells. The aberrant activation of the proteasome has been widely observed in various types of cancers and implicated in the development and progression of carcinogenesis. In the era of targeted therapies, the clinical use of proteasome inhibitors necessitates a better understanding of the molecular mechanisms of cell death responsible for their cytotoxic action, which are reviewed here in the context of sensitization of malignant gliomas, a tumor type particularly refractory to conventional treatments.

[642]

TÍTULO / TITLE: - Prognostic value of interleukin-8 and MMP-9 in nasopharyngeal carcinoma.

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

REVISTA / JOURNAL: - Eur Arch Otorhinolaryngol. 2013 Jun 9.

- Enlace al texto completo (gratis o de pago) [1007/s00405-013-2580-](http://1007/s00405-013-2580-3)

[3](#)

AUTORES / AUTHORS: - Cheng D; Kong H; Li Y

INSTITUCIÓN / INSTITUTION: - Department of Transfusion, The First Hospital of China Medical University, North Nanjing Street, No. 155, Shenyang, 110001, Liaoning Province, People's Republic of China, dayecheng_cmu@yahoo.cn.

RESUMEN / SUMMARY: - Nasopharyngeal carcinoma (NPC) is one of the leading causes of cancer related death in China. One of the reasons is the absence of tumor specific prognostic markers. The aim of this study was to examine the prognostic values of interleukin-8 (IL-8) and matrix metalloproteinase-9 (MMP-9) in NPC patients. A total of 99 consecutive NPC patients and 40 healthy controls were recruited for this study. Serum levels of IL-8 and MMP-9 were evaluated in NPC patients who were followed up for 5 years. The serum levels of IL-8 and MMP-9 in NPC patients were significantly higher than those in healthy controls (IL-8 26.3 [2.9-68.0] ng/ml vs. 20.3 [2.3-38.6] ng/ml, $P < 0.001$; MMP-9 23.5 [3.6-52.1] ng/ml vs. 17.3 [2.6-36.9] ng/ml, $P = 0.002$), respectively. The serum levels of IL-8 and MMP-9 were positively correlated with the N classification (IL-8, $P = 0.041$, and MMP-9, $P < 0.001$, respectively) and clinical stage (IL-8, $P = 0.022$, and MMP-9, $P < 0.001$, respectively) in NPC patients. Analysis using the Kaplan-Meier method indicated that patients with high levels of IL-8 or MMP-9 had significantly shorter overall survival (OS) (IL-8, $P = 0.012$; MMP-9, $P < 0.001$) and disease-free survival (DFS) (IL-8, $P = 0.021$; MMP-9, $P = 0.003$) time than those with low levels of MMP-9 or IL-8. Univariate and multivariate analysis revealed elevated MMP-9 level was an independent predictor of shorter OS and DFS. Both MMP-9 and IL-8 are involved in NPC progression. MMP-9 in serum may be the clinically useful indicator for prognostic evaluation in NPC patients.

[643]

TÍTULO / TITLE: - Targeted paclitaxel nanoparticles modified with follicle-stimulating hormone beta 81-95 peptide show effective antitumor activity against ovarian carcinoma.

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

REVISTA / JOURNAL: - Int J Pharm. 2013 Sep 10;453(2):498-505. doi: 10.1016/j.ijpharm.2013.06.038. Epub 2013 Jun 25.

- Enlace al texto completo (gratis o de pago)

1016/j.ijpharm.2013.06.038

AUTORES / AUTHORS: - Zhang X; Chen J; Kang Y; Hong S; Zheng Y; Sun H; Xu C

INSTITUCIÓN / INSTITUTION: - Obstetrics and Gynecology Hospital, Fudan University, Shanghai 200433, People's Republic of China; Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai 200011, People's Republic of China.

RESUMEN / SUMMARY: - The majority of patients with advanced ovarian cancer will experience a relapse and ultimately die from refractory diseases. Targeted therapy shows promise for these patients. Novel therapeutic strategies should be developed on the basis of the molecular mechanisms involved in ovarian cancer and the steroid hormone environment of ovaries. The ovary is the main target organ of follicle-stimulating hormone (FSH), which bind to its receptor with high affinity. In this study a FSH receptor-targeting ligand, FSH beta 81-95 peptide, was used as a targeting moiety to synthesize an FSH receptor-mediated drug delivery system. FSH beta 81-95 peptide-conjugated nanoparticles (FSH81-NPs) and paclitaxel-loaded FSH81-NPs (FSH81-NP-PTXs) were synthesized. In vitro studies showed that FSH beta 81-95 peptide enabled the specific uptake of cytotoxic drugs and increased the intracellular paclitaxel concentration in FSH receptor-expressing cancer cells, resulting in enhanced cytotoxic effects. In vivo studies showed that FSH81-NP-PTXs possessed higher antitumor efficacy against FSH receptor-expressing tumors without any clinical signs of adverse side effects or body weight loss due to modification with FSH beta 81-95 peptide. Therefore, FSH binding peptide-targeted drug delivery system exhibited high potential in the treatment of ovarian cancer, and tumor targeting via reproductive hormone receptors might improve the outcome of diseases.

[644]

TÍTULO / TITLE: - A phase I study of histone deacetylase inhibitor, pracinostat (SB939), in pediatric patients with refractory solid tumors: IND203 a trial of the NCIC IND program/C17 pediatric phase I consortium.

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

REVISTA / JOURNAL: - *Pediatr Blood Cancer*. 2013 Jul 25. doi: 10.1002/pbc.24694.

●● [Enlace al texto completo \(gratis o de pago\) 1002/pbc.24694](#)

AUTORES / AUTHORS: - Zorzi AP; Bernstein M; Samson Y; Wall DA; Desai S; Nicky D; Wainman N; Eisenhauer E; Baruchel S

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Department of Pediatrics, Children's Hospital, Western University, London, ON, Canada.

RESUMEN / SUMMARY: - **BACKGROUND:** Pracinostat (SB939) is a potent oral inhibitor of class 1, 2, and 4 histone deacetylases (HDAC). The adult recommended phase II dose (RP2D) is 60 mg po three times per week (t.i.w.) for 3 weeks every 4 weeks. This study assessed the toxicities and

pharmacokinetics of pracinostat and determined the RP2D in children with refractory solid tumors. METHODS: Pediatric patients with refractory solid tumors were treated with oral pracinostat t.i.w. for 3 consecutive weeks, followed by 1 week off dosing. Three dose levels-25, 35, and 45 mg/m² were evaluated using a standard 3 + 3 cohort design. Pharmacokinetic (PK) studies were optional. RESULTS: Twelve patients were enrolled. The most common diagnosis was Ewing sarcoma. Most adverse events (AEs) were hematological with five (40%) patients experiencing grade 3 neutropenia. Non-hematological AEs were generally grade 1. No dose limiting toxicities occurred. More hematological and non-hematological AEs occurred at 45 mg/m² : Two of five patients experienced Grade 3 neutropenia and one each Grade 3 thrombocytopenia and leucopenia, Grade 1 fatigue and anorexia occurred in three. The RP2D was declared to be 45 mg/m² (comparable to an adult dose of 80 mg). One patient had a best response of stable disease (duration of 2.9 months). Three patients on 25 mg/m² and one each on 35 and 45 mg/m² participated in the PK study. No dose related changes in C_{max} or AUC occurred. CONCLUSIONS: Pracinostat is reasonably well tolerated in children with refractory solid tumors. The RP2D is 45 mg/m² . *Pediatr Blood Cancer* © 2013 Wiley Periodicals, Inc.

[645]

TÍTULO / TITLE: - SC-535, a Novel Oral Multikinase Inhibitor, Showed Potent Antitumor Activity in Human Melanoma Models.

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

REVISTA / JOURNAL: - *Cell Physiol Biochem.* 2013;32(1):138-53. doi: 10.1159/000350123. Epub 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1159/000350123](#)

AUTORES / AUTHORS: - Chen X; Ji P; Yang HW; Yang LL; Zhou S; Zhong L; Ma S; Fu XY; Zhou C; Li GB; Zheng MW; Wei YQ; Yang SY

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan, China.

RESUMEN / SUMMARY: - Background: Melanoma is considered as one of the most aggressive and deadliest cancers and current targeted therapies of melanoma often suffer limited efficacy or drug resistance. Discovery of novel multikinase inhibitors as anti-melanoma drug candidates is still needed. Methods: In this investigation, we assessed the in vitro and in vivo anti-melanoma activities of SC-535, which is a novel small molecule multikinase inhibitor discovered by us recently. We analyzed inhibitory effects of SC-535 on various melanoma cell lines and human umbilical vascular endothelial cells (HUVEC) in vitro. Tumor xenografts in athymic mice were used to examine the in vivo activity of SC-535. Results: SC-535 could efficiently inhibit vascular endothelial growth factor receptor (VEGFR) 1/2/3, B-RAF, and C-RAF kinases.

It showed significant antiangiogenic potencies both in vitro and in vivo and considerable anti-proliferative ability against several melanoma cell lines. Oral administration of SC-535 resulted in dose-dependent suppression of tumor growth in WM2664 and C32 xenograft mouse models. Studies of mechanisms of action indicated that SC-535 suppressed the tumor angiogenesis and induced G2/M phase cell cycle arrest in human melanoma cells. SC-535 possesses favorable pharmacokinetic properties. Conclusion: All of these results support SC-535 as a potential candidate for clinical studies in patients with melanoma.

[646]

TÍTULO / TITLE: - Monitoring of Plasma Cell-Free DNA in Predicting Postoperative Recurrence of Clear Cell Renal Cell Carcinoma.

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

REVISTA / JOURNAL: - Urol Int. 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago) [1159/000351409](#)

AUTORES / AUTHORS: - Wan J; Zhu L; Jiang Z; Cheng K

INSTITUCIÓN / INSTITUTION: - Operation Center, Third Xiangya Hospital of Central-South University, Changsha, PR China.

RESUMEN / SUMMARY: - Background: Circulating cell-free DNA (cfDNA) mostly originates from tumors and its level correlates with treatment. We assessed whether the level of plasma cfDNA could help monitor recurrence after nephrectomy. Methods: This study included 92 patients with clear cell renal cell carcinoma (cRCC). Quantitative real-time PCR was used to measure the level of plasma cfDNA before and after nephrectomy. Results: The pretreatment level of plasma cfDNA in patients with metastatic cRCC (6.04 +/- 0.72) was significantly higher than in those with localized cRCC (5.29 +/- 0.53, p = 0.017) or controls (0.65 +/- 0.29, p < 0.001). Of patients with localized cRCC, those with recurrence had a significantly higher plasma cfDNA level than those without (p = 0.024). The patients with a high plasma cfDNA level had a significantly higher recurrence rate than those with a low plasma cfDNA level before and after nephrectomy (p = 0.018). Conclusion: The level of plasma cfDNA may be useful as a tool to monitor patients during follow-up and guide further diagnostic work-up for the detection of recurrence. © 2013 S. Karger AG, Basel.

[647]

TÍTULO / TITLE: - Induction of HepG2 cell apoptosis by Irgarol 1051 through mitochondrial dysfunction and oxidative stresses.

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

REVISTA / JOURNAL: - Toxicol In Vitro. 2013 May 28;27(6):1771-1779. doi: 10.1016/j.tiv.2013.05.006.

●● Enlace al texto completo (gratis o de pago) 1016/j.tiv.2013.05.006

AUTORES / AUTHORS: - Wang L; Liang B; Li L; Liu W

INSTITUCIÓN / INSTITUTION: - Marine Biology Institute, Shantou University, Shantou, Guangdong 515063, PR China.

RESUMEN / SUMMARY: - In this study, HepG2 cells were exposed to 0.04-40mg/L Irgarol 1051. Results show that Irgarol 1051 can damage cell morphology and cause a significant decrease in cell viability. Positive staining by Annexin V, caspase-3 activity enhancement, and the damage in cell ultrastructure indicated an apoptotic mode of cell death for 4.0mg/L Irgarol 1051 treatment. At the same time, caspase-9 was also significantly induced by 0.4 and 4.0mg/L Irgarol 1051 at 72h, which suggests that the intrinsic mitochondria pathway was involved in the apoptosis. The mitochondrial membrane potential decreased significantly after the HepG2 cells were exposed to Irgarol 1051 for 6 and 72h. Especially, the translocation of cytochrome c from mitochondria to cytosol was recorded, supporting the idea that the mitochondrial pathway was involved in the apoptosis signal pathways induced by Irgarol 1051. The significantly increased levels of intracellular reactive oxygen species (ROS) and an immediate ROS burst were also recorded. The results here may imply that Irgarol 1051 induces HepG2 cell apoptosis through mitochondrial dysfunction and oxidative stresses. Although it is possible that this chemical has no detrimental effects on human health at the environmentally relevant concentration, it may cause problems to top coastal predators due to bio-accumulation through the food chain.

[648]

TÍTULO / TITLE: - Casticin Induces Human Glioma Cell Death through Apoptosis and Mitotic Arrest.

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

REVISTA / JOURNAL: - Cell Physiol Biochem. 2013;31(6):805-14. doi: 10.1159/000350098. Epub 2013 Jun 3.

●● Enlace al texto completo (gratis o de pago) 1159/000350098

AUTORES / AUTHORS: - Liu E; Kuang Y; He W; Xing X; Gu J

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, General Hospital of People's Liberation Army Chengdu Military Region, Chengdu.

RESUMEN / SUMMARY: - Background: Malignant gliomas are the leading cause of morbidity and mortality in brain and central nervous system tumors. Recently, casticin has drawn wide attention to its critical role in tumor progression. However, the effect of casticin on glioma remains undefined. Methods: Following treatment with casticin, cell viability, apoptosis, and cell cycle arrest were examined in U251 glioma cells. Additionally, the involved molecular mechanism was assessed by western blotting and flow cytometry. Results: Casticin triggered an obvious dose-dependent decrease in U251, U87 and U373 glioma cell viability, and the growth inhibitory effect of casticin was

correlated with cell cycle arrest and cell apoptosis. Further mechanistic analysis indicated that casticin induced G2/M phase arrest by attenuating the polymerization of tubulin. Furthermore, striking apoptosis was also confirmed, accompanied by the up-regulation of caspase-3, p53 and proapoptotic protein Bax. These effects were absent when the caspase inhibitor z-VAD-fmk or p53 inhibitor PFTalpha were applied, suggesting that casticin could trigger cell apoptosis in a caspase-3 and p53-dependent manner. Conclusion: These findings provide a prominent insight into how casticin abrogates the pathogenesis of glioma, and support its potential clinical prospect for further development of anti-brain cancer therapy.

[649]

TÍTULO / TITLE: - The utility of prostate-specific antigen in the management of advanced prostate cancer.

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

REVISTA / JOURNAL: - BJU Int. 2013 Sep;112(5):548-60. doi: 10.1111/bju.12061. Epub 2013 Jul 4.

●● Enlace al texto completo (gratis o de pago) [1111/bju.12061](#)

AUTORES / AUTHORS: - Crawford ED; Bennett CL; Andriole GL; Garnick MB; Petrylak DP

INSTITUCIÓN / INSTITUTION: - University of Colorado School of Medicine, Aurora, CO, USA.

RESUMEN / SUMMARY: - To review current prostate-specific antigen (PSA) metrics used in monitoring treatment of advanced prostate cancer, with a specific focus on castration-resistant prostate cancer (CRPC) therapies. Explore what is known about the correlation between PSA and androgen levels as well as underlying reasons for persistent PSA expression and serum elevation in CRPC, and outline suggestions for use of PSA in managing patients with advanced prostate cancer. A comprehensive search of the PubMed database for English language articles through April 2012 was performed using the following Medical Subject Headings (MeSH) keywords or terms, alone or in combination: 'prostate cancer'; 'prostate cancer treatment'; 'prostate cancer outcomes'; 'prostate-specific antigen'; 'androgen receptor'; 'advanced prostate cancer'; 'castration-resistant prostate cancer'; 'biomarkers'. Bibliographies of relevant articles were searched for additional references. Relevant medical society and regulatory agency web sites from the USA and Europe were accessed for issued guidance on PSA use. PSA doubling time (PSADT) is a useful metric for determining which patients should be considered for androgen-deprivation therapy (ADT) after failing local treatment or for second-line therapies after failing ADT. However, it is not a validated surrogate for survival and no therapy has received regulatory approval based upon PSADT characteristics. PSA nadir and time-to-nadir have been identified as possible prognostic markers for patients receiving ADT. There is no universally accepted

definition for PSA progression, nor is PSA progression a regulatory-approved surrogate for clinical progression in drug approval trials. PSA responses to second-line therapies can vary and are not considered by regulatory agencies as valid surrogates for clinical endpoints, so they must be assessed in the context of each individual therapy and trial design. PSA expression in CRPC is often a reflection of persistent androgen receptor activity. While we can provide guidance for use of PSA monitoring in managing patients with advanced prostate cancer based on the data at hand, there is an urgent need for prospective analyses of refined PSA metrics in conjunction with newer prostate cancer biomarkers in clinical trials to provide stronger evidence for their roles as surrogate endpoints.

[650]

TÍTULO / TITLE: - NVP-BEZ235, Dual Phosphatidylinositol 3-Kinase/Mammalian Target of Rapamycin Inhibitor, Prominently Enhances Radiosensitivity of Prostate Cancer Cell Line PC-3.

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

REVISTA / JOURNAL: - Cancer Biother Radiopharm. 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) 1089/cbr.2012.1443

AUTORES / AUTHORS: - Zhu W; Fu W; Hu L

INSTITUCIÓN / INSTITUTION: - 1 Department of Radiation Oncology, Cancer Center, Qilu Hospital affiliated to Shandong University, Jinan, China.

RESUMEN / SUMMARY: - Abstract Background: Aberrant activation of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway may account for development of radioadaptation and is not rare in prostate cancer. Neither PI3K nor mTOR blockade could completely inhibit the pathway owing to paradoxical feedback, so we anticipate dual PI3K/mTOR blockade by NVP-BEZ235 to radiosensitize prostate cancer cells. Methods: We investigated into the radiosensitizing effect of NVP-BEZ235 on PC-3 cells, which are devoid of androgen receptors. Clonogenic survival and MTT assays were performed, and to pursue underlying cellular changes flowcytometric analysis of cell cycle and apoptosis as well as western blot were carried out. Results: Exposure to NVP-BEZ235 and irradiation caused a greater degree of survival inhibition than ionizing radiation (IR) or BEZ235 alone. Dual PI3K/mTOR blockade along with IR induced a G2/M arrest and enhanced proapoptotic effect. NVP-BEZ235 radiosensitized PC-3 cells through counteracting constitutive as well as IR-triggered activation of Akt/mTOR signaling. Conclusions: Our study demonstrated that the dual PI3K/mTOR inhibitor NVP-BEZ235 prominently improved the radiosensitivity of PC-3 cells. It sensitized tumor cells to irradiation via interruption of cell cycle progression and augmentation of cell apoptosis, which was due to its constraint on constitutive and IR-elicited PI3K/Akt/mTOR signaling activation.

[651]

TÍTULO / TITLE: - Phosphatidylinositol 3-kinases inhibitor LY294002 potentiates the cytotoxic effects of doxorubicin, vincristine, and etoposide in a panel of cancer cell lines.

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

REVISTA / JOURNAL: - Fundam Clin Pharmacol. 2013 Jun 17. doi: 10.1111/fcp.12043.

●● Enlace al texto completo (gratis o de pago) [1111/fcp.12043](#)

AUTORES / AUTHORS: - Badinloo M; Esmaeili-Mahani S

INSTITUCIÓN / INSTITUTION: - Physiology Research Center, Kerman University of Medical Sciences, Jihad Blvd, 7619813159, Kerman, Iran.

RESUMEN / SUMMARY: - Many novel therapeutic approaches to overcome chemoresistance have involved targeting specific signaling pathways such as the phosphatidylinositol 3-kinase (PI3K) pathway. PI3K is a known stress response pathway which is involved in the regulation of cell survival, apoptosis, and growth. Inhibition of this pathway may possibly restore or augment the effectiveness of chemotherapy. Using three human malignant cell lines, we examined the effects of LY294002 (PI3K inhibitor) on chemotherapeutic agent-induced apoptosis and cytotoxicity. An antimicrotubule agent vincristine, a topoisomerase II inhibitor etoposide, and a DNA cross-linking agent doxorubicin were used accompanied with LY294002. Cell viability was determined by MTT assay, and the induction of apoptosis was assessed by immunoblotting of caspase-3. Blocking the PI3K/Akt cascade with a PI3K inhibitor LY294002 (10 µM) increased the cytotoxic effect of vincristine and doxorubicin on SK-OV-3 cell line. Furthermore, LY294002 showed a greater promoting effect in etoposide- and doxorubicin-induced cytotoxicity on MDA-MB-468 and A549 cells. The quantity of cleaved caspase-3 in cancer cells that had combination therapy was increased compared with that in the cells treated with each drug alone. We suggest that inhibitors of the PI3K/Akt pathway in combination with chemotherapeutic agents may induce cell death effectively and be a potent modality to treat various types of cancer. The effectiveness of such combination therapy is depending to the used cell line and class of anticancer drug.

[652]

TÍTULO / TITLE: - Intraperitoneal administration of cisplatin via an in situ cross-linkable hyaluronic acid-based hydrogel for peritoneal dissemination of gastric cancer.

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

REVISTA / JOURNAL: - Surg Today. 2013 Jul 26.

●● Enlace al texto completo (gratis o de pago) [1007/s00595-013-0674-](#)

[6](#)

AUTORES / AUTHORS: - Emoto S; Yamaguchi H; Kamei T; Ishigami H; Suhara T; Suzuki Y; Ito T; Kitayama J; Watanabe T

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan, semoto-ky@umin.ac.jp.

RESUMEN / SUMMARY: - **PURPOSE:** To develop a drug-delivery system for the prolonged retention of intraperitoneally (i.p.) administered cisplatin (CDDP) to deliver intraperitoneal chemotherapy against peritoneal carcinomatosis effectively. **METHODS:** CDDP was encapsulated inside an in situ cross-linkable hyaluronic acid (HA)-based hydrogel. The gelation and degradation kinetics of the hydrogel and the release kinetics of CDDP were investigated in vitro, and the antitumor effect was investigated in a mouse model of peritoneal dissemination of human gastric cancer. **RESULTS:** The gelation time varied according to the concentration of two polymers: HA-adipic dihydrazide and HA-aldehyde. CDDP was released from the hydrogel for more than 4 days. A cell proliferation assay showed that the polymers themselves were not cytotoxic toward MKN45P, a human gastric cancer cell line. By mixing the two polymers in the peritoneum, in situ gelation was achieved. The weight of peritoneal nodules decreased in the hydrogel-conjugated CDDP group, whereas no significant antitumor effect was observed in the free CDDP group. **CONCLUSIONS:** In situ cross-linkable HA hydrogels represent a promising biomaterial to prolong the retention and sustain the release of intraperitoneally administered CDDP in the peritoneal cavity and to enhance its antitumor effects against peritoneal dissemination.

[653]

TÍTULO / TITLE: - A randomized phase II pre-surgical trial of weekly low-dose tamoxifen versus raloxifene versus placebo in premenopausal women with estrogen receptor positive breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Breast Cancer Res. 2013 Jun 20;15(3):R47.

●● [Enlace al texto completo \(gratis o de pago\) 1186/bcr3439](#)

AUTORES / AUTHORS: - Serrano D; Lazzeroni M; Gandini S; Macis D; Johansson H; Gjerde J; Lien E; Feroce I; Pruneri G; Sandri MT; Bassi F; Brenelli F; Luini A; Cazzaniga M; Varricchio CM; Guerrieri-Gonzaga A; Decensi A; Bonanni B

RESUMEN / SUMMARY: - **INTRODUCTION:** We previously demonstrated that 1 or 5 mg per day of tamoxifen (T) given for 4 weeks before surgery reduces Ki-67 in breast cancer (BC) patients to the same extent as the standard 20 mg/d. Given the long half-life of T, a weekly dose (10mg/w) may be worth testing. Also, raloxifene® has shown Ki-67 reduction in post menopausal patients in a preoperative setting, but data in premenopausal women are limited. We conducted a randomized trial testing T 10mg per week (w), vs R 60 mg/d vs placebo in a pre-surgical model. **METHODS:** Out of 204 screened subjects, 57

were not eligible, 22 refused to participate and 125 were included in the study. The participants were all premenopausal women with estrogen receptor-positive BC. They were randomly assigned to either T 10mg/w or R 60 mg/d or placebo for 6 weeks before surgery. The primary endpoint was tissue change of Ki67. Secondary endpoints were modulation of estrogen and progesterone receptors and several other circulating biomarkers. RESULTS: Ki-67 was not significantly modulated by either treatment. In contrast, both selective estrogen receptor modulators (SERMs) significantly modulated circulating IGF-I/IGFBP-3 ratio, cholesterol, fibrinogen and anti-thrombin III. Estradiol was increased with both SERMs. Within the tamoxifen arm, CYP2D6 polymorphism analysis showed a higher concentration of N-desTamoxifen, one of the tamoxifen metabolites, in subjects with reduced CYP2D6 activity. Moreover, a reduction of Ki67 and a marked increase of sex hormone binding protein (SHBP) were observed in the active phenotype. CONCLUSIONS: A weekly dose of tamoxifen and a standard dose of raloxifene did not inhibit tumor cell proliferation, measured as Ki67 expression, in premenopausal BC patients. However in the tamoxifen arm women with an extensive phenotype for CYP2D6 reached a significant Ki67 modulation.

[654]

TÍTULO / TITLE: - Colorectal carcinoma-derived fibroblasts modulate natural killer cell phenotype and antitumor cytotoxicity.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Med Oncol. 2013 Sep;30(3):663. doi: 10.1007/s12032-013-0663-z. Epub 2013 Jul 20.

●● Enlace al texto completo (gratis o de pago) [1007/s12032-013-0663-](#)

[Z](#)

AUTORES / AUTHORS: - Li T; Yi S; Liu W; Jia C; Wang G; Hua X; Tai Y; Zhang Q; Chen G

INSTITUCIÓN / INSTITUTION: - Department of Hepatic Surgery, The 3rd Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

RESUMEN / SUMMARY: - Substantial evidence indicates that cancer-associated fibroblasts (CAFs) are critical components in the process of cancer progression. However, the role of CAFs in the immunopathogenesis of human cancer remains elusive. In this study, we demonstrate that purified colorectal carcinoma-derived fibroblasts exhibit activated phenotypes characterized by substantial alpha-smooth muscle actin expression. These CAFs sharply suppress natural killer (NK) cell functions in co-culture experiments. In contrast, normal skin fibroblasts had only a minimal effect on NK cell phenotype and function. Moreover, we demonstrated that prostaglandin E2 (PGE2) was released by fibroblasts in co-culture experiments. Thus, the functional modulation of NK cells by CAFs may represent a novel mechanism linking the pro-inflammatory response to immune tolerance within the tumor milieu.

[655]

TÍTULO / TITLE: - Tumor Reoxygenation Following Administration of the EGFR Inhibitor, Gefitinib, in Experimental Tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Adv Exp Med Biol. 2013;789:265-71. doi: 10.1007/978-1-4614-7411-1_36.

●● Enlace al texto completo (gratis o de pago) [1007/978-1-4614-7411-1_36](#)

AUTORES / AUTHORS: - Karroum O; Kengen J; Gregoire V; Gallez B; Jordan BF
INSTITUCIÓN / INSTITUTION: - Biomedical Magnetic Resonance Group, Louvain Drug Research Institute, Universite catholique de Louvain, Av.Mounier 73.40, 1200, Brussels, Belgium.

RESUMEN / SUMMARY: - It is well recognized that tumor hypoxia is a critical determinant for response to therapy. The effect of an EGFR inhibitor/gefitinib (Iressa®) on tumor oxygenation was monitored daily using in vivo EPR (electron paramagnetic resonance) oximetry on TLT and FSall tumor models. An increase in pO₂ was shown at a dose of 45 mg/kg i.p. (n = 4/group/tumor model). This allowed the identification of a window of reoxygenation in both tumor models (with a maximum between 15 and 20 mmHg after 2 days of treatment). The increase in tumor oxygenation was shown to be the result of a decrease in oxygen consumption. This is the first report on the effect of gefitinib on oxygen consumption by tumor cells and subsequent increase in tumor oxygenation in vivo.

[656]

TÍTULO / TITLE: - Angiopoietins and non-vascular endothelial growth factor antiangiogenic targets in advanced renal cell carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer J. 2013 Jul-Aug;19(4):307-10. doi: 10.1097/PPO.0b013e31829d5d15.

●● Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e31829d5d15](#)

AUTORES / AUTHORS: - Richey SL; Hutson TE

INSTITUCIÓN / INSTITUTION: - From the *Hematology and Oncology, Texas Oncology Fort Worth, Fort Worth, TX; and daggerTexas Oncology, PA GU Oncology Program, Baylor-Sammons Cancer Center, Dallas, TX.

RESUMEN / SUMMARY: - The treatment of metastatic renal cell carcinoma has evolved from an era dominated by immune modulation to an era of antiangiogenesis agents. Blockade of vascular endothelial growth factor-mediated pathways and mammalian target of rapamycin pathways has accounted for most of these gains. Although these agents have offered

dramatic improvements in survival for kidney cancer patients, resistance inevitably occurs, and new classes of agents are needed to continue to improve outcomes in this setting. We discuss several alternative pathways of angiogenesis, which are being investigated as targets to overcome treatment resistance, including angiopoietin family proteins, fibroblast growth factor, platelet-derived growth factor, and vascular disrupting agents.

[657]

TÍTULO / TITLE: - Antitumoral effects of 9-cis retinoic acid in adrenocortical cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Mol Life Sci. 2013 Jun 27.

●● Enlace al texto completo (gratis o de pago) [1007/s00018-013-1408-](http://dx.doi.org/10.1007/s00018-013-1408-z)

[Z](#)

AUTORES / AUTHORS: - Szabo DR; Baghy K; Szabo PM; Zsippai A; Marczell I; Nagy Z; Varga V; Eder K; Toth S; Buzas EI; Falus A; Kovalszky I; Patocs A; Racz K; Igaz P

INSTITUCIÓN / INSTITUTION: - 2nd Department of Medicine, Faculty of Medicine, Semmelweis University, Szentkiralyi Str. 46, Budapest, 1088, Hungary.

RESUMEN / SUMMARY: - The currently available medical treatment options of adrenocortical cancer (ACC) are limited. In our previous meta-analysis of adrenocortical tumor genomics data, ACC was associated with reduced retinoic acid production and retinoid X receptor-mediated signaling. Our objective has been to study the potential antitumoral effects of 9-cis retinoic acid (9-cisRA) on the ACC cell line NCI-H295R and in a xenograft model. Cell proliferation, hormone secretion, and gene expression have been studied in the NCI-H295R cell line. A complex bioinformatics approach involving pathway and network analysis has been performed. Selected genes have been validated by real-time qRT-PCR. Athymic nude mice xenografted with NCI-H295R have been used in a pilot in vivo xenograft model. 9-cisRA significantly decreased cell viability and steroid hormone secretion in a concentration- and time-dependent manner in the NCI-H295R cell line. Four major molecular pathways have been identified by the analysis of gene expression data. Ten genes have been successfully validated involved in: (1) steroid hormone secretion (HSD3B1, HSD3B2), (2) retinoic acid signaling (ABCA1, ABCG1, HMGCR), (3) cell-cycle damage (GADD45A, CCNE2, UHRF1), and the (4) immune response (MAP2K6, IL1R2). 9-cisRA appears to directly regulate the cell cycle by network analysis. 9-cisRA also reduced tumor growth in the in vivo xenograft model. In conclusion, 9-cisRA might represent a promising new candidate in the treatment of hormone-secreting adrenal tumors and adrenocortical cancer.

[658]

TÍTULO / TITLE: - Phase 2 trial of erlotinib with or without PF-3512676 (CPG 7909, a Toll-like receptor 9 agonist) in patients with advanced recurrent EGFR-positive non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jul 1;14(7):557-63. doi: 10.4161/cbt.24598. Epub 2013 May 10.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.24598](#)

AUTORES / AUTHORS: - Belani CP; Nemunaitis JJ; Chachoua A; Eisenberg PD; Raez LE; Cuevas JD; Mather CB; Benner RJ; Meech SJ

INSTITUCIÓN / INSTITUTION: - Penn State Hershey Cancer Institute; Milton S. Hershey Medical Center; Hershey, PA USA.

RESUMEN / SUMMARY: - This phase 2 study assessed PF-3512676 plus erlotinib in patients with epidermal growth factor receptor-positive advanced non-small cell lung cancer after prior chemotherapy failure. Patients were randomized 1:1 to PF-3512676 (0.20 mg/kg injected subcutaneously once weekly) plus erlotinib (150 mg daily) or erlotinib alone. The primary objective was to estimate progression-free survival (PFS). Patients received PF-3512676 plus erlotinib (n = 18) or erlotinib alone (n = 21). The study was halted because an unplanned interim analysis indicated that large improvement in PFS with addition of PF-3512676 would be unlikely. In the PF-3512676-plus-erlotinib and erlotinib-alone arms, median PFS was 1.6 and 1.7 mo (hazard ratio, 1.00; 95% confidence interval, 0.5-2.0; P = 0.9335), respectively. Salient grade ≥ 3 adverse events in PF-3512676-plus-erlotinib and erlotinib-alone arms were diarrhea (5/0), dyspnea (5/6), fatigue (4/1), other flu-like symptoms (2/0), anemia (2/1), and lymphocytopenia (based on laboratory values, $\frac{1}{4}$). Adding PF-3512676 to erlotinib did not show potential for increased progression-free survival over erlotinib alone in patients with advanced recurrent epidermal growth factor receptor-positive non-small cell lung cancer.

[659]

TÍTULO / TITLE: - "One marker does not fit all": additional translational and validation studies are needed to identify faithful predictors of pemetrexed activity in mesothelioma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug;8(8):e79-80. doi: 10.1097/JTO.0b013e318293e45b.

●● Enlace al texto completo (gratis o de pago)

[1097/JTO.0b013e318293e45b](#)

AUTORES / AUTHORS: - Giovannetti E; Peters GJ; Zucali PA

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, VU University Medical Center, De Boelelaan, Amsterdam, The Netherlands Department of Medical Oncology and Hematology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy.

[660]

TÍTULO / TITLE: - Clinicopathological features among patients with advanced human epidermal growth factor-2-positive breast cancer with prolonged clinical benefit to first-line trastuzumab-based therapy: a retrospective cohort study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Breast Cancer. 2013 Aug;13(4):254-63. doi: 10.1016/j.clbc.2013.02.010.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.clbc.2013.02.010](#)

AUTORES / AUTHORS: - Vaz-Luis I; Seah D; Olson EM; Wagle N; Metzger-Filho O; Sohl J; Litsas G; Burstein HJ; Krop IE; Winer EP; Lin NU

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Dana-Farber Cancer Institute, Breast Oncology Center, Boston, MA; Clinical and Translational Oncology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal.

RESUMEN / SUMMARY: - BACKGROUND: The magnitude of benefit of trastuzumab for the treatment of advanced HER2-positive breast cancer varies widely. In this retrospective study, we investigated the clinicopathological features associated with prolonged first-line trastuzumab-based treatment duration. PATIENTS AND METHODS: A total of 164 patients diagnosed with advanced HER2-positive breast cancer and treated with first-line trastuzumab-based therapy from 1999 to 2009 were identified. Duration of treatment was classified according to tertiles. Different logistic regression models including age, disease-free interval, number of metastatic sites, visceral disease, hormone receptor, and adjuvant trastuzumab were fitted to investigate associations with benefit of prolonged trastuzumab-based therapies. The predictive value of each model was assessed using C-statistics. RESULTS: At a median follow-up of 5.8 years (range, 0.7-22.1 years), patients in the short-, intermediate-, and long-term treatment duration groups were given first-line trastuzumab-based therapy for < 7.2 months, 7.2 to 14 months, and > 14 months, respectively. In the multivariate analysis, patients with long-term clinical benefit had a higher likelihood of having hormone receptor-positive tumors (odds ratio [OR]positive vs. negative = 2.39 [95% confidence interval (CI), 1.08-5.31]; P = .032); and a lower likelihood of having received adjuvant trastuzumab (ORadjuvant trastuzumab vs. no adjuvant trastuzumab = 0.30 [95% CI, 0.10-0.96]; P = .043]. C-statistics varied between 0.634 and 0.699. CONCLUSION: Long-term benefit of trastuzumab-based therapy is associated with hormone receptor positivity and the absence of previous adjuvant trastuzumab. Nevertheless, clinicopathological features had a low predictive value for prolonged treatment duration. The validation of the current findings and the identification of molecular features associated the magnitude of trastuzumab benefit should be encouraged.

[661]

TÍTULO / TITLE: - EZH2 Promotes E2F-Driven SCLC Tumorigenesis through Modulation of Apoptosis and Cell-Cycle Regulation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Thorac Oncol. 2013 Aug;8(8):1102-6. doi: 10.1097/JTO.0b013e318298762f.

●● Enlace al texto completo (gratis o de pago)

[1097/JTO.0b013e318298762f](#)

AUTORES / AUTHORS: - Hubaux R; Thu KL; Coe BP; Macaulay C; Lam S; Lam WL

INSTITUCIÓN / INSTITUTION: - Integrative Oncology, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada.

RESUMEN / SUMMARY: - INTRODUCTION: Although enhancer of zeste homolog 2 (EZH2) has been associated with both non-small cell and small-cell lung cancers (SCLCs), current observations suggest different mechanisms of EZH2 activation and overexpression in these lung cancer types. Globally, SCLC kills 200,000 people yearly. New clinical approaches for SCLC treatment are required to improve the poor survival rate. Given the therapeutic potential of EZH2 as a target, we sought to delineate the downstream consequences of EZH2 disruption to identify the cellular mechanisms by which EZH2 promotes tumorigenesis in SCLC. METHODS: We generated cells with stable expression of short hairpin RNA targeting EZH2 and corresponding controls (pLKO.1) and determined the consequences of EZH2 knockdown on the cell cycle and apoptosis by means of propidium iodide staining and fluorescence-activated cell sorting, Western blot, quantitative reverse transcriptase-polymerase chain reaction as well as cell viability assessment using methylthiazol tetrazolium assays. RESULTS: We discovered that EZH2 inhibition (1) increased apoptotic activity by up-regulating the proapoptotic factors Puma and Bad, (2) decreased the fraction of cells in S or G2/M phases, and (3) elevated p21 protein levels, implicating EZH2 in cell death and cell-cycle control in SCLC. CONCLUSION: Our findings present evidence for the role of EZH2 in the regulation of cell cycle and apoptosis, providing a biological mechanism to explain the tumorigenicity of EZH2 in SCLC. Our work points to the great potential of EZH2 as a therapeutic target in SCLC.

[662]

TÍTULO / TITLE: - Histone deacetylase inhibitors and epigenetic modifications as a novel strategy in renal cell carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer J. 2013 Jul-Aug;19(4):333-40. doi: 10.1097/PPO.0b013e3182a09e07.

- Enlace al texto completo (gratis o de pago)

[1097/PPO.0b013e3182a09e07](#)

AUTORES / AUTHORS: - Ramakrishnan S; Pili R

INSTITUCIÓN / INSTITUTION: - From the Genitourinary Program and Department of Cancer Pathology and Prevention, Roswell Park Cancer Institute, Buffalo, NY.

RESUMEN / SUMMARY: - Recent investigations of renal cell carcinoma (RCC) have revealed several epigenetic modifications, as well as alterations in the genes and enzymes that regulate these changes. Preclinical models have revealed that histone gene modifiers and epigenetic alterations may play a critical role in RCC tumorigenesis. Specific changes in DNA methylation and mutations of histone modifiers have been identified and may be associated with an aggressive phenotype. In addition, the potential of reversing the effects of these enzymes and hence reversing the cellular epigenetic landscape to a "normal phenotype" have led to an increasing interest in developing targeted chromatin remodeling agents. However, the translation of the understanding of these changes to the clinic for the treatment of RCC has posed significant challenges, partly due to tumor heterogeneity. This review describes the aberrant histone and DNA alterations recently reported in RCC and highlights the potential targeted chromatin remodeling therapies in the management of this disease.

[663]

TÍTULO / TITLE: - Correlation Between Quantitative HER-2 Protein Expression and Risk for Brain Metastases in HER-2+ Advanced Breast Cancer Patients Receiving Trastuzumab-Containing Therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncologist. 2013;18(6):775. doi: 10.1634/theoncologist.2011-0212erratum.

- Enlace al texto completo (gratis o de pago)

[1634/theoncologist.2011-0212erratum](#)

AUTORES / AUTHORS: - Duchnowska R; Biernat W; Szostakiewicz B; Sperinde J; Piette F; Haddad M; Paquet A; Lie Y; Czartoryska-Arlukowicz B; Wysocki P; Jankowski T; Radecka B; Foszczynska-Kloda M; Litwiniuk M; Debska S; Weidler J; Huang W; Buyse M; Bates M; Jassem J

[664]

- CASTELLANO -

TÍTULO / TITLE: Prognostische Bedeutung der VEGF- und FLT-1-Expression bei Patienten mit lokal fortgeschrittenem Plattenepithelkarzinom der Kopf-Hals-Region.

TÍTULO / TITLE: - Prognostic impact of VEGF and FLT-1 receptor expression in patients with 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;189(8):639-646. Epub 2013 Jun 9.

- [Enlace al texto completo \(gratis o de pago\) 1007/s00066-013-0341-](#)

[2](#)

AUTORES / AUTHORS: - Seibold ND; Schild SE; Gebhard MP; Noack F; Rades D

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Lubeck, Ratzeburger Allee 160, 23538, Lubeck, Germany.

RESUMEN / SUMMARY: - **BACKGROUND AND PURPOSE:** This study investigated the prognostic value of tumor cell expression of vascular endothelial growth factor (VEGF) and its receptor fms-related tyrosine kinase 1 (FLT-1) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who had been treated with adjuvant radiotherapy or radiochemotherapy. **MATERIAL AND METHODS:** The impact of tumor cell VEGF and FLT-1 expression plus 11 additional factors on loco-regional control (LRC), metastases-free survival (MFS) and overall survival (OS) was retrospectively evaluated in 157 patients. The additional factors were age, gender, performance status, pre-radiotherapy (pre-RT) hemoglobin levels, tumor site, histologic grade, T-category, N-category, human papillomavirus (HPV) status, extent of resection and chemotherapy. **RESULTS:** On multivariate analysis, improved LRC was significantly associated with an absence of VEGF expression (risk ratio, RR: 5.02; $p = 0.009$), lower T-category (RR: 2.00; $p < 0.001$), lower N-category (RR: 3.75; $p < 0.001$) and pre-RT hemoglobin levels ≥ 12 g/dl (RR: 2.20; $p = 0.029$). Improved MFS was significantly associated with an absence of VEGF expression (RR: 7.46; $p = 0.002$), lower T-category (RR: 1.97; $p = 0.002$), lower N-category (RR: 3.29; $p = 0.005$) and a favorable tumor location (RR: 1.34; $p = 0.033$); HPV positivity showed a trend towards improved MFS (RR: 1.43; $p = 0.09$). Improved OS was significantly associated with an absence of VEGF expression (RR: 3.22; $p = 0.041$), pre-RT hemoglobin levels ≥ 12 g/dl (RR: 2.47; $p = 0.009$), lower T-category (RR: 1.92; $p < 0.001$) and lower N-category (RR: 3.39; $p < 0.001$). FLT-1 expression was significantly associated with LRC and OS in the univariate but not in the multivariate analysis. **CONCLUSION:** VEGF expression proved to be an independent negative predictor for LRC, MFS and OS in patients treated for locally advanced SCCHN with adjuvant radiotherapy or radiochemotherapy. FLT-1 expression was not significant in multivariate analyses.

[665]

TÍTULO / TITLE: - Randomized Phase II Trial of Weekly vs. Every 2 Weeks vs. Every 3 Weeks Nanoparticle Albumin-Bound Paclitaxel With Bevacizumab as First-Line Chemotherapy for Metastatic Breast Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Breast Cancer. 2013 Aug;13(4):239-246.e1. doi: 10.1016/j.clbc.2013.02.008.

●● Enlace al texto completo (gratis o de pago) [1016/j.clbc.2013.02.008](#)

AUTORES / AUTHORS: - Seidman AD; Conlin AK; Bach A; Moynahan ME; Lake D; Forero A; Wright GS; Hackney MH; Clawson A; Norton L; Hudis CA

INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, Department of Medicine, Division of Solid Tumor Oncology, New York, NY. Electronic address: seidmana@mskcc.org.

RESUMEN / SUMMARY: - BACKGROUND: Nanoparticle albumin-bound paclitaxel (nab-P) and bevacizumab have each demonstrated efficacy in patients with MBC. This trial was designed to further develop nab-P by evaluating its efficacy and safety using every 3 weeks (q3w), every 2 weeks (q2w), or weekly scheduling in combination with bevacizumab as first-line treatment of MBC. PATIENTS AND METHODS: This open-label phase II study randomized patients to nab-P 260 mg/m² q3w (arm A) vs. 260 mg/m² q2w with filgrastim (arm B) vs. 130 mg/m² weekly uninterrupted, all with bevacizumab (15 mg/kg q3w arm A, 10 mg/kg q2w arms B and C). The primary endpoints were overall response rate (ORR) and toxicity. Time to tumor progression (TTP) and overall survival were secondary endpoints. RESULTS: Of 212 patients randomized, 208 (arm A, 75; arm B, 54; arm C, 79) were treated. Arm B was closed early due to toxicity, with more grade ≥ 2 fatigue (arm A, 46%; arm B, 62%; arm C, 62%) and bone pain (arm A, 11%; arm B, 23%; arm C, 5%). Neurotoxicity grade ≥ 2 was equivalent across the arms ($> 50\%$) and reversible for most patients. Febrile neutropenia occurred in $\leq 3\%$ of patients in all arms. ORR was similar among the arms (arm A, 45%; arm B, 41%; arm C, 46%). Median TTP was slightly longer in arm C (9.0 months) vs. arms A (8.0 months) and B (5.8 months) (overall, $P = .105$). CONCLUSIONS: Significant antitumor activity was observed in all the arms. Weekly nab-P with bevacizumab appeared to have the highest therapeutic index. However, sensory neuropathy was treatment limiting, which suggests that a 3 weeks on and 1 week off schedule should be explored.

[666]

TÍTULO / TITLE: - Gene expression signature-based prognostic risk score in patients with glioblastoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Sci. 2013 Jun 7. doi: 10.1111/cas.12214.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12214](#)

AUTORES / AUTHORS: - Kawaguchi A; Yajima N; Tsuchiya N; Homma J; Sano M; Natsumeda M; Takahashi H; Fujii Y; Kakuma T; Yamanaka R

INSTITUCIÓN / INSTITUTION: - Biostatistic Center, Kurume University School of Medicine, Kurume, Japan.

RESUMEN / SUMMARY: - The present study aimed to identify genes associated with patient survival to improve our understanding of the underlying biology of gliomas. We investigated whether the expression of genes selected using random survival forests models could be used to define glioma subgroups more objectively than standard pathology. The RNA from 32 non-treated grade 4 gliomas were analyzed using the GeneChip Human Genome U133 Plus 2.0 Expression array (which contains approximately 47 000 genes). Twenty-five genes whose expressions were strongly and consistently related to patient survival were identified. The prognosis prediction score of these genes was most significant among several variables and survival analyses. The prognosis prediction score of three genes and age classifiers also revealed a strong prognostic value among grade 4 gliomas. These results were validated in an independent samples set (n = 488). Our method was effective for objectively classifying grade 4 gliomas and was a more accurate prognosis predictor than histological grading.

[667]

TÍTULO / TITLE: - Gender-specific profiling in SCN1A polymorphisms and time-to-recurrence in patients with stage II/III colorectal cancer treated with adjuvant 5-fluoruracil chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics J. 2013 Jun 11. doi: 10.1038/tpj.2013.21.

●● [Enlace al texto completo \(gratis o de pago\) 1038/tpj.2013.21](#)

AUTORES / AUTHORS: - Benhaim L; Gerger A; Bohanes P; Paez D; Wakatsuki T; Yang D; Labonte MJ; Ning Y; El-Khoueiry R; Loupakis F; Zhang W; Laurent-Puig P; Lenz HJ

INSTITUCIÓN / INSTITUTION: - 1] Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles CA, USA [2] INSERM_UMR-S 775, Bases moléculaires de la réponse aux xenobiotiques, Université Paris Descartes, Paris, France.

RESUMEN / SUMMARY: - This study was designed to analyze the gender-related association between SCN1A polymorphisms (voltage-gated sodium channels; alpha-subunit) and time-to-recurrence (TTR) in patients with colorectal cancer (CRC) treated with 5-fluoruracil (5-FU)-based adjuvant chemotherapy. We enrolled from a prospective database patients with stage II and III CRC treated with adjuvant 5-FU-based chemotherapy. Genotypes for SCN1A rs3812718 and rs229877 were determined by direct DNA sequencing. One hundred twenty-seven males and 107 females were included in the study. In the univariate and multivariate analysis, the shortest TTR was associated with female patients carrying the rs3812718-TT genotype (hazard ratio (HR): 2.26 (95% confidence interval (CI): 0.89, 5.70), P=0.039) but with male patients carrying the

rs3812718-CC genotype (HR: 0.49 (95% CI: 0.18, 1.38), P=0.048). For rs229877 the CT genotype was associated with a trend for shorter TTR in both gender populations. The study validated gender-dependent association between genomic SCN1A rs3812718 polymorphism and TTR in CRC patients treated with adjuvant 5-FU-based chemotherapy. This study confirms that voltage-gated Na⁺ channels may be a potential therapeutic target and a useful predictive biomarker before 5-FU infusion. The Pharmacogenomics Journal advance online publication, 11 June 2013; doi:10.1038/tpj.2013.21.

[668]

- CASTELLANO -

TÍTULO / TITLE: Der Fibroblastenwachstumsfaktor 2 ist von prognostischer Bedeutung bei Patienten mit lokal fortgeschrittenem Plattenepithelkarzinom der Kopf-Hals-Region.

TÍTULO / TITLE: - Fibroblast growth factor 2 is of prognostic value for patients with locally advanced squamous cell carcinoma of the head and neck.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Strahlenther Onkol. 2013 Jul 18.

●● Enlace al texto completo (gratis o de pago) [1007/s00066-013-0368-](http://1007/s00066-013-0368-4)

[4](#)

AUTORES / AUTHORS: - Rades D; Seibold ND; Gebhard MP; Noack F; Schild SE

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Lubeck, Ratzeburger Allee 160, 23538, Lubeck, Germany, rades.dirk@gmx.net.

RESUMEN / SUMMARY: - BACKGROUND AND PURPOSE: Patients with locally advanced SCCHN have a poor prognosis. This study investigated the prognostic value of the tumor cell expression of the fibroblast growth factor 2 (FGF-2) in patients treated with surgery followed by radiotherapy. PATIENTS AND METHODS: The impact of FGF-2-expression and 11 additional potential prognostic factors on loco-regional control (LRC), metastases-free survival (MFS), and overall survival (OS) was retrospectively evaluated in 146 patients. Additional factors included age, gender, performance status, pre-radiotherapy hemoglobin levels, tumor site, histologic grade, T-category, N-category, human papilloma virus (HPV) status, extent of resection, and chemotherapy. Univariate analyses were performed with the Kaplan-Meier method and the log-rank test, multivariate analyses with the Cox proportional hazard model. RESULTS: On multivariate analysis, improved LRC was significantly associated with FGF-2-negativity [risk ratio (RR): 7.33; 95 %-confidence interval (CI): 2.88-19.05; p < 0.001], lower T-category (RR: 2.42; 95 %-CI: 1.47-4.33; p < 0.001), lower N-category (RR: 12.36; 95 %-CI: 3.48-78.91; p < 0.001), and pre-radiotherapy hemoglobin levels \geq 12 g/dl (RR: 4.18; 95 %-CI: 1.73-10.53; p = 0.002). No factor was significantly associated with improved MFS. Lower T-category showed a trend (RR: 1.59; 95 %-CI: 0.97-2.82; p = 0.069). Better OS was

significantly associated with FGF-2-negativity (RR: 5.10; 2.22-11.80; $p < 0.001$), lower T-category (RR: 2.17; 95 %-CI: 1.38-3.68; $p < 0.001$), lower N-category (RR: 3.86; 95 %-CI: 1.60-10.85; $p = 0.002$), and pre-radiotherapy hemoglobin levels ≥ 12 g/dl (RR: 3.20; 95 %-CI: 1.46-7.30; $p = 0.004$). HPV-positivity showed a trend (RR: 2.36; 95 %-CI: n.a.; $p = 0.054$). CONCLUSIONS: Tumor cell expression of FGF-2 proved to be an independent prognostic factor for LRC and OS. This factor can help personalize treatment and stratify patients in future trials.

[669]

TÍTULO / TITLE: - Apoptotic Circulating Tumor Cells (CTCs) in early and metastatic breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jun 18.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1167](#)

AUTORES / AUTHORS: - Kallergi G; Konstantinidis G; Markomanolaki H; Papadaki MA; Mavroudis D; Stournaras C; Georgoulas V; Agelaki S

INSTITUCIÓN / INSTITUTION: - 1Laboratory of Tumor Cell Biology, Medical School, University of Crete.

RESUMEN / SUMMARY: - The detection of circulating tumor cells (CTCs) in breast cancer is strongly associated with disease relapse. Since it is unclear if all CTCs are capable to generate metastasis, we investigated their apoptotic and proliferative status in 56 CTC-positive (29 early and 27 metastatic) breast cancer (BC) patients. Double staining immunofluorescence (IF) experiments were performed in peripheral blood mononuclear cells (PBMC) cytopins, using the pancytokeratin A45-B/B3 antibody and either M30 (apoptotic marker) or Ki67 (proliferation marker) antibodies. Apoptosis was also evaluated using a polycaspase detection kit. Patients with metastatic disease had significantly lower numbers of apoptotic CTCs compared to early breast cancer patients (polycaspase kit: 8.1% vs 47.4% of the total CTC number; $p=0.0001$; M30-antibody: 32.1% vs 76.63%; $p=0.002$). The median percentage of apoptotic CTCs per patient was also lower in patients with advanced compared to those with early disease (polycaspase kit: 0% vs 53.6%; M30-antibody: 15% vs 80%). Ki67 positive CTCs were identified in 51.7% and 44% of patients with early and metastatic disease, respectively. Adjuvant chemotherapy reduced both the number of CTCs/patient and the number of proliferating CTCs (63.9% vs 30%). In conclusion apoptotic CTCs could be detected in patients with BC irrespectively of their clinical status, though the incidence of detection is higher in early compared to metastatic patients. The detection of CTCs which survive despite adjuvant therapy implies that CTC elimination should be attempted using agents targeting their distinctive molecular characteristics.

[670]

TÍTULO / TITLE: - Alterations of axis inhibition protein 1 (AXIN1) in hepatitis B virus-related hepatocellular carcinoma and overexpression of AXIN1 induces apoptosis in hepatocellular cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Res. 2013;20(7):281-8.

AUTORES / AUTHORS: - Li J; Quan H; Liu Q; Si Z; He Z; Qi H

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Second Xiangya Hospital, Central South University, Changsha, China.

ljjiequn2002@hotmail.com

RESUMEN / SUMMARY: - Axis inhibition protein 1 (AXIN1) is a negative regulator of Wnt/beta-catenin signaling via regulating the level of beta-catenin. However, the role of AXIN1 in the tumorigenesis and progression of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) is less clear. PCR sequence analysis, immunohistochemistry, and Western blot were performed on 22 HBV-related HCC samples and corresponding nontumor liver tissues to detect variants in AXIN1 gene and the expression level of AXIN1. Human hepatoma cell lines SNU475 and SNU423 were transfected with pCDNA3.1-AXIN1-myc or AXIN1 G425S-myc mutant. The growth curve and apoptosis rate of cell lines, phosphorylation of beta-catenin, and cell cycle regulatory proteins depending on beta-catenin transcriptional activity were detected. We identified four mutations of AXIN1 in 22 primary HBV-related HCCs and demonstrated a lower expression of AXIN1 in HBV-related HCC tissues than that in paired adjacent nontumor tissues. Overexpression of AXIN1 wild-type but not AXIN1 mutant inhibited the growth of HCC cell lines, accelerated their apoptosis, and negatively regulated beta-catenin-dependent transcriptional activity. Our study revealed that alterations of AXIN1 were involved in HBV-related HCC. Overexpression of AXIN1 but not AXIN1 mutant negatively regulated beta-catenin-dependent transcriptional activity and downregulated the level of cell cycle regulatory proteins, suggesting that AXIN1 may be a potential target for gene therapy of primary HCC.

[671]

TÍTULO / TITLE: - Which is false: Oxaliplatin or fluoropyrimidine? An analysis of patients with KRAS wild-type metastatic colorectal cancer treated with first-line epidermal growth factor receptor monoclonal antibody.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Sci. 2013 Jul 3. doi: 10.1111/cas.12224.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cas.12224](#)

AUTORES / AUTHORS: - Wen F; Tang R; Sang Y; Li M; Hu Q; Du Z; Zhou Y; Zhang P; He X; Li Q

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

RESUMEN / SUMMARY: - This meta-analysis was performed to determine whether the addition of monoclonal antibodies (mAbs) of epidermal growth factor receptor (EGFR) to oxaliplatin-based chemotherapy treatment improves efficacy in KRAS wild-type metastatic colorectal cancer (mCRC), and whether infusional 5-fluorouracil (5-FU) and oxaliplatin is a preferred combination for EGFR mAbs. Oxaliplatin (including treatment), EGFR mAbs, first-line treatment, KRAS wild-type, and mCRC were used as key words. The PRIME, OPUS, COIN, and NORDIC VII trials were identified by two independent authors. Time-to-event outcomes of overall survival (OS) and progression-free survival (PFS) were analyzed using HRs (hazard ratios) with fixed effect, and response rate (RR) using odd ratios (OR) with fixed effect. A total of 1767 patients who were KRAS wild-type were included in this meta-analysis, with 866 patients in the mAbs and chemotherapy combination group and 901 patients in the chemotherapy alone group. The addition of mAbs to oxaliplatin-based chemotherapy in patients with KRAS wild-type mCRC as first-line treatment resulted in significant improvements in PFS (HR = 0.88; 95% confidence interval (CI), 0.79-0.99; P = 0.03) and response rate (RR) (OR = 1.38; 95% CI, 1.14-1.66; P = 0.009) compared with chemotherapy alone, but the difference in OS was not significant (HR = 0.96; 95% CI, 0.85-1.08; P = 0.48). However, the differences in OS and PFS were not significant when mAbs were added to bolus 5-FU or capecitabine-based regimens compared with chemotherapy alone, whereas PFS improved with an infusional 5-FU and oxaliplatin combination (P = 0.06; PFS, HR = 0.76; 95% CI, 0.65-0.86; P = 0.0002), and even OS was marginally significant, which was consistent with the subgroup analysis of cetuximab and panitumumab. EGFR mAbs combined with oxaliplatin and an infusional 5-FU regimen was associated with significantly improved RR, PFS and OS as first-line treatment in KRAS wild-type mCRC.

[672]

TÍTULO / TITLE: - Circulating Tumor Cells Following First Chemotherapy Cycle: An Early and Strong Predictor of Outcome in Patients With Metastatic Breast Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncologist. 2013 Jul 19.

●● Enlace al texto completo (gratis o de pago)

[1634/theoncologist.2012-0479](#)

AUTORES / AUTHORS: - Martin M; Custodio S; de Las Casas ML; Garcia-Saenz JA; de la Torre JC; Bellon-Cano JM; Lopez-Tarruella S; Vidaurreta-Lazaro M; de la Orden V; Jerez Y; Marquez-Rodas I; Casado A; Sastre J; Diaz-Rubio E

INSTITUCIÓN / INSTITUTION: - Medical Oncology Service and.

RESUMEN / SUMMARY: - We investigated the prognostic significance of circulating tumor cells (CTCs) determined immediately before the second cycle of chemotherapy in patients with metastatic breast cancer (MBC). The CTC counts were taken at baseline, before the first cycle of chemotherapy (CTC-0) and on day 21 before commencing the second cycle of chemotherapy (CTC-21) in consecutive MBC patients. The study's primary objectives were to analyze relationships between CTC-21 count and overall survival (OS). Based on the current literature, the CTC measurements were dichotomized as 0-4 versus ≥ 5 CTCs. Of 117 patients recruited, 99 were evaluable. Patients with 0-4 CTCs on day 21 had a significantly better OS than those with ≥ 5 CTCs (median OS: 38.5 months vs. 8.7 months). They also had a significantly better progression-free survival (PFS; median: 9.4 months vs. 3.0 months) and clinical benefit rate (77% vs. 44%). The OS of patients whose baseline CTCs were ≥ 5 but dropped to < 5 on day 21 was apparently similar to those who had < 5 CTCs at baseline. In a Cox regression analysis, CTC-21 was the only independent variable significantly predicting OS and PFS. Our data indicate that CTCs determined immediately before the second cycle of chemotherapy is an early and strong predictor of treatment outcome in MBC patients.

[673]

TÍTULO / TITLE: - Contradictory KRAS mutation test results in a patient with metastatic colon cancer: A clinical dilemma in the era of personalized medicine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 12;14(8).

AUTORES / AUTHORS: - Lamparella NE; Saroya BS; Yang Z; Sarwani NE; El-Deiry WS

INSTITUCIÓN / INSTITUTION: - Department of Medicine; Division of Hematology/Oncology; Penn State Hershey Cancer Institute; Hershey, PA USA.

RESUMEN / SUMMARY: - The KRAS oncogene is mutated in 40-50% of colorectal cancers and confers resistance to EGFR-targeted therapy. In the clinic, agents such as cetuximab or panitumumab target the EGFR receptor for therapeutic benefit. Cetuximab was approved by the FDA in 2012 as first-line therapy for KRAS mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer, in combination with FOLFIRI (5-Fluorouracil, Irinotecan, Leucovorin). Herein we report a case of metastatic colon cancer with conflicting testing results for KRAS oncogene from two different reference laboratories. The discordant reports complicated the decision-making process regarding administration of targeted anti-EGFR personalized therapy. As the second test result was wild-type from the same original pathological specimen, the patient was treated with cetuximab-containing combination chemotherapy and appeared to have a response after prior disease progression. It is unclear whether the observed response was fully due to regression of wild-type KRAS-

containing tumor or any component of antibody-dependent cellular cytotoxicity to a heterogeneous tumor in this patient.

[674]

TÍTULO / TITLE: - F-FDG PET/CT predicts survival in patients with inflammatory breast cancer undergoing neoadjuvant chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Nucl Med Mol Imaging. 2013 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1007/s00259-013-2506-](#)

[8](#)

AUTORES / AUTHORS: - Carkaci S; Sherman CT; Ozkan E; Adrada BE; Wei W; Rohren EM; Mawlawi OR; Ueno NT; Buchholz TA; Yang WT

INSTITUCIÓN / INSTITUTION: - Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX, 77030, USA, selincarkaci@msn.com.

RESUMEN / SUMMARY: - PURPOSE: The objective of this study was to evaluate the role of 18F-FDG PET/CT in predicting overall survival in inflammatory breast cancer patients undergoing neoadjuvant chemotherapy. METHODS: Included in this retrospective study were 53 patients with inflammatory breast cancer who had at least two PET/CT studies including a baseline study before the start of neoadjuvant chemotherapy. Univariate and multivariate analyses were performed to assess the effects on survival of the following factors: tumor maximum standardized uptake value (SUVmax) at baseline, preoperatively and at follow-up, decrease in tumor SUVmax, histological tumor type, grade, estrogen, progesterone, HER2/neu receptor status, and extent of disease at presentation including axillary nodal and distant metastases. RESULTS: By univariate analysis, survival was significantly associated with decrease in tumor SUVmax and tumor receptor status. Patients with decrease in tumor SUVmax had better survival (P = 0.02). Patients with a triple-negative tumor (P = 0.0006), a Her2/neu-negative tumor (P = 0.038) or an ER-negative tumor (P = 0.039) had worse survival. Multivariate analysis confirmed decrease in tumor SUVmax and triple-negative receptor status as significant predictors of survival. Every 10 % decrease in tumor SUVmax from baseline translated to a 15 % lower probability of death, and complete resolution of tumor FDG uptake translated to 80 % lower probability of death (P = 0.014). Patients with a triple-negative tumor had 4.11 times higher probability of death (P = 0.004). CONCLUSION: Decrease in tumor SUVmax is an independent predictor of survival in patients with inflammatory breast cancer undergoing neoadjuvant chemotherapy. Further investigation with prospective studies is warranted to clarify its role in assessing response and altering therapy.

[675]

TÍTULO / TITLE: - Danitumumab adjunctive therapy. No place in either first- or second-line treatment of metastatic colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Prescrire Int. 2013 May;22(138):120.

RESUMEN / SUMMARY: - Adding panitumumab to standard protocols does not prolong survival but provokes additional adverse effects.

[676]

TÍTULO / TITLE: - Prognostic significance of tumor-associated trypsin inhibitor (TATI) and human chorionic gonadotropin-beta (hCGbeta) in patients with hepatocellular carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Scand J Gastroenterol. 2013 Jul 29.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[3109/00365521.2013.805810](#)

AUTORES / AUTHORS: - Lyytinen I; Lempinen M; Nordin A; Makisalo H; Stenman UH; Isoniemi H

INSTITUCIÓN / INSTITUTION: - Department of Transplantation and Liver Surgery, Clinic of Surgery, Helsinki University Hospital, Helsinki, Finland.

RESUMEN / SUMMARY: - Abstract Aim. Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most frequent cause of cancer death worldwide. The aim of this study was to evaluate the prognostic value of serum tumor-associated trypsin inhibitor (TATI) and the free beta subunit of human chorionic gonadotropin (hCGbeta) in patients with HCC. Methods. The serum concentrations of TATI and hCGbeta were determined by time-resolved immunofluorometric assays (IFMA) in pretreatment serum samples from 144 patients with HCC. Clinical data were retrieved from patient records and survival data obtained from Statistics Finland. Results. The overall cumulative disease-specific survival was 69% at 1 year, 50% at 2 years and 33% at 5 years. Disease-specific median survival time was 26 months. The overall survival in patients with low serum concentrations of TATI or hCGbeta was statistically significantly better than in patients with elevated concentrations ($p = 0.003$ and 0.003 , respectively). In multivariate analysis, both serum TATI and serum hCGbeta were independent prognostic markers. Conclusion. The results imply that elevated serum concentrations of TATI and hCGbeta are predictors of adverse prognosis in patients with HCC and appear to be useful adjuncts in predicting prognosis in patients with HCC.

[677]

TÍTULO / TITLE: - B-cell receptor signaling inhibitors for treatment of autoimmune inflammatory diseases and B-cell malignancies.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int Rev Immunol. 2013;32(4):397-427. doi: 10.3109/08830185.2013.818140.

●● Enlace al texto completo (gratis o de pago)

[3109/08830185.2013.818140](https://doi.org/10.3109/08830185.2013.818140)

AUTORES / AUTHORS: - Puri KD; Di Paolo JA; Gold MR

INSTITUCIÓN / INSTITUTION: - 1Gilead Sciences, Inc. , Seattle, WA , USA.

RESUMEN / SUMMARY: - B-cell receptor (BCR) signaling is essential for normal B-cell development, selection, survival, proliferation, and differentiation into antibody-secreting cells. Similarly, this pathway plays a key role in the pathogenesis of multiple B-cell malignancies. Genetic and pharmacological approaches have established an important role for the Spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (Btk), and phosphatidylinositol 3-kinase isoform p110delta (PI3Kdelta) in coupling the BCR and other BCRs to B-cell survival, migration, and activation. In the past few years, several small-molecule inhibitory drugs that target PI3Kdelta, Btk, and Syk have been developed and shown to have efficacy in clinical trials for the treatment of several types of B-cell malignancies. Emerging preclinical data have also shown a critical role of BCR signaling in the activation and function of self-reactive B cells that contribute to autoimmune diseases. Because BCR signaling plays a major role in both B-cell-mediated autoimmune inflammation and B-cell malignancies, inhibition of this pathway may represent a promising new strategy for treating these diseases. This review summarizes recent achievements in the mechanism of action, pharmacological properties, and clinical activity and toxicity of these BCR signaling inhibitors, with a focus on their emerging role in treating lymphoid malignancies and autoimmune disorders.

[678]

TÍTULO / TITLE: - Medical mistrust influences black women's level of engagement in BRCA ½ genetic counseling and testing.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Natl Med Assoc. 2013 Spring;105(1):17-22.

AUTORES / AUTHORS: - Sheppard VB; Mays D; LaVeist T; Tercyak KP

INSTITUCIÓN / INSTITUTION: - Cancer Control Program, Lombardi Cancer Center, Department of Oncology, Georgetown University Medical Center, Washington, District of Columbia 20007, USA. vls3@georgetown.edu

RESUMEN / SUMMARY: - Clinical evidence supports the value of BRCA1/2 genetic counseling and testing for managing hereditary breast and ovarian cancer risk; however, BRCA1/2 genetic counseling and testing are underutilized among black women, and reasons for low use remain elusive. We examined the potential influence of sociocultural factors (medical mistrust, concerns about genetic discrimination) on genetic counseling and testing engagement in a sample of 100 black women at increased risk for carrying a BRCA1/2 mutation. Eligible participants fell into 1 of 3 groups: (1) healthy

women with at least 1 first-degree relative affected by breast and/or ovarian cancer, (2) women diagnosed with breast cancer at age less than or equal to 50 years; and (3) women diagnosed with breast and/or ovarian cancer at age greater than or equal to 50 years with either 1 first-degree relative or 2 second-degree relatives with breast and/or ovarian cancer. Participants were recruited from clinical and community settings and completed a semistructured interview. Study variable relationships were examined using bivariate tests and multivariate regression analysis. As expected, genetic counseling and testing engagement among this sample was low (28%). After accounting for sociodemographic factors and self-efficacy ($\beta=0.37$, $p<.001$), women with higher medical mistrust had lower genetic counseling and testing engagement ($\beta=-0.26$, $p<.01$). Community-level and individual interventions are needed to improve utilization of genetic counseling and testing among underserved women. Along with trust building between patients and providers, strategies should enhance women's personal confidence. The impact of medical mistrust on the realization of the benefits of personalized medicine in minority populations should be further examined in future studies.

[679]

TÍTULO / TITLE: - Receptor tyrosine kinases MET and RON as prognostic factors in diffuse large B-cell lymphoma patients receiving R-CHOP.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Sci. 2013 Jun 7. doi: 10.1111/cas.12215.

●● Enlace al texto completo (gratis o de pago) [1111/cas.12215](#)

AUTORES / AUTHORS: - Koh YW; Hwang HS; Jung SJ; Park C; Yoon DH; Suh C; Huh J

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea.

RESUMEN / SUMMARY: - Receptor tyrosine kinases MET and RON (MST1R) form non-covalent complexes on the cell surface, a critical step in tumor progression. A recent study suggested a prognostic role for MET expression in diffuse large B-cell lymphoma (DLBCL). The aim of this study was to examine the impact of MET and RON expression in uniformly treated DLBCL patients. The expression of MET and RON was retrospectively examined by immunohistochemistry in 120 DLBCL patients treated with rituximab combined with a CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone). The median follow-up time was 42.5 months (range, 1-89 months). Thirty-two (26%) and 30 patients (25%) expressed MET or RON, respectively. Seventy-five patients (62.5%) were negative for both MET and RON (MET- RON-). MET negativity was associated with worse overall survival ($P = 0.029$). In multivariate analysis, negativity for both MET and RON (MET- RON-) was strongly associated with inferior overall survival ($P = 0.008$). Interestingly, the MET- RON- phenotype retained its prognostic impact after subgroup analysis

according to the international prognostic index or by the cell of origin by immunohistochemical algorithm by Choi et al. This study suggests that the MET- RON- phenotype is an independent prognostic factor in DLBCL patients receiving R-CHOP, and may identify a subgroup of DLBCL patients who require more intensive therapy.

[680]

TÍTULO / TITLE: - Gene panel model predictive of outcome in patients with prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - OMICS. 2013 Aug;17(8):407-13. doi: 10.1089/omi.2012.0124. Epub 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago) [1089/omi.2012.0124](#)

AUTORES / AUTHORS: - Rabiau N; Dantal Y; Guy L; Ngollo M; Dagdemir A; Kemeny JL; Terris B; Vieillefond A; Boiteux JP; Bignon YJ; Bernard-Gallon D

INSTITUCIÓN / INSTITUTION: - 1 Department of Oncogenetics, Centre Jean Perrin , Clermont-Ferrand, France .

RESUMEN / SUMMARY: - Abstract In men at high risk for prostate cancer, established clinical and pathological parameters provide only limited prognostic information. Here we analyzed a French cohort of 103 prostate cancer patients and developed a gene panel model predictive of outcome in this group of patients. The model comprised of a 15-gene TaqMan Low-Density Array (TLDA) card, with gene expressions compared to a standardized reference. The RQ value for each gene was calculated, and a scoring system was developed. Summing all the binary scores (0 or 1) corresponding to the 15 genes, a global score is obtained between 0 and 15. This global score can be compared to Gleason score (0 to 10) by recalculating it into a 0-10 scaled score. A scaled score ≥ 2 suggested that the patient is suffering from a prostate cancer, and a scaled score ≥ 7 flagged aggressive cancer. Statistical analyses demonstrated a strongly significant linear correlation ($p=3.50E-08$) between scaled score and Gleason score for this prostate cancer cohort (N=103). These results support the capacity of this designed 15 target gene TLDA card approach to predict outcome in prostate cancer, opening up a new avenue for personalized medicine through future independent replication and applications for rapid identification of aggressive prostate cancer phenotypes for early intervention.

[681]

TÍTULO / TITLE: - Predictive biomarkers may help individualize treatment for patients with follicular lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - CA Cancer J Clin. 2013 Jul 10. doi: 10.3322/caac.21197.

●● Enlace al texto completo (gratis o de pago) [3322/caac.21197](#)

AUTORES / AUTHORS: - Barton MK

[682]

TÍTULO / TITLE: - Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Cancer Care (Engl). 2013 Jun 3. doi: 10.1111/ecc.12068.

●● Enlace al texto completo (gratis o de pago) [1111/ecc.12068](#)

AUTORES / AUTHORS: - Ergun M; Eyigor S; Karaca B; Kisim A; Uslu R

INSTITUCIÓN / INSTITUTION: - Physical Therapy and Rehabilitation Dept, Ege University Faculty of Medicine, Izmir.

RESUMEN / SUMMARY: - The aim of this study was to explore the effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in patients who completed breast cancer treatment. Sixty breast cancer patients were randomised into three groups, as supervised exercise group, home exercise group and education group. Angiogenesis and apoptosis-related cytokine levels and quality of life (EORTC QOL-C30: European Organisation for Research and Treatment of Cancer Quality of Life C30), fatigue (Brief Fatigue Inventory) and depression (BDI: Beck Depression Inventory) scores were compared before and after a 12-week exercise programme. After the exercise programme, statistically significant decreases were found in interleukin-8 and neutrophil activating protein-78 levels in the home exercise group ($P < 0.05$). The education group showed a statistically significant increase in monocyte chemoattractant protein-1 level ($P < 0.05$). Functional score and global health score of EORTC QOL-C30 in the supervised exercise group and functional score of EORTC QOL-C30 in the home exercise group increased significantly after exercise programme ($P < 0.05$). BDI score was significantly lower in the supervised exercise group after the exercise programme ($P < 0.05$). Changes in angiogenesis and apoptosis-related molecules in the study groups suggest a possible effect of exercise on these parameters. Exercise programmes are safe and effective on quality of life and depression in breast cancer patients whose treatments are complete.

[683]

TÍTULO / TITLE: - Clinical relevance of pharmacogenetics in gastrointestinal stromal tumor treatment in the era of personalized therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Jun;14(8):941-56. doi: 10.2217/pgs.13.63.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.63](#)

AUTORES / AUTHORS: - Angelini S; Ravegnini G; Fletcher JA; Maffei F; Hrelia P

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy & Biotechnology, Via Irnerio 48, 40126 Alma Mater Studiorum-University of Bologna, Bologna, Italy. s.angelini@unibo.it

RESUMEN / SUMMARY: - Gastrointestinal stromal tumor (GIST) is a well-recognized and now relatively well-understood mesenchymal tumor. Before the imatinib era, the treatment of metastatic GIST was frustrating owing to its refractoriness to conventional chemotherapy and radiotherapy. After a metastatic GIST patient was granted compassionate use of imatinib in 2000, the treatment of this disease has emerged as a model for the development of other molecularly targeted therapies. In this article the authors review how tumor genotypes, in particular KIT and PDGFRA mutational analysis, have been integrated in the optimal clinical management of GIST patients. The authors also discuss the potential practical relevance of pharmacogenetics, which, integrated with therapeutic drug monitoring, should receive greater consideration, with the aim of personalized therapy.

[684]

TÍTULO / TITLE: - Amyloid precursor-like protein 2 suppresses irradiation-induced apoptosis in Ewing sarcoma cells and is elevated in immune-evasive Ewing sarcoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 21;14(8).

AUTORES / AUTHORS: - Peters HL; Yan Y; Nordgren TM; Cutucache CE; Joshi SS; Solheim JC

INSTITUCIÓN / INSTITUTION: - Eppley Institute for Research in Cancer and Allied Diseases; University of Nebraska Medical Center; Omaha, NE USA.

RESUMEN / SUMMARY: - Despite surgery, chemotherapy and radiotherapy treatments, the children, adolescents and young adults who are diagnosed with metastasized Ewing sarcoma face a dismal prognosis. Amyloid precursor-like protein 2 (APLP2) has recently been implicated in the survival of cancer cells and in our current study, APLP2's contribution to the survival of Ewing sarcoma cells was examined. APLP2 was readily detected in all Ewing sarcoma cell lines analyzed by western blotting, with the TC71 Ewing sarcoma cells expressing the lowest level of APLP2 among the lines. While irradiation induces apoptosis in TC71 Ewing sarcoma cells (as we determined by quantifying the proportion of cells in the sub-G 1 population), transfection of additional APLP2 into TC71 decreased irradiation-induced apoptosis. Consistent with these findings, in parallel studies, we noted that isolates of the TC71 cell line that survived co-culture with lymphokine-activated killer (LAK) cells (which kill by inducing apoptosis in target cells) displayed increased expression of APLP2, in addition to smaller sub-G 1 cell populations after irradiation. Together, these findings suggest that APLP2 lowers the sensitivity of Ewing sarcoma cells to

radiotherapy-induced apoptosis and that APLP2 expression is increased in Ewing sarcoma cells able to survive exposure to cytotoxic immune cells.

[685]

TÍTULO / TITLE: - Quantitative changes in p53, Bcl-2 and apoptosis in blood and urine of bladder cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lab. 2013;59(3-4):349-58.

AUTORES / AUTHORS: - El-Gamal EM; Gouda MS

INSTITUCIÓN / INSTITUTION: - Urology and Nephrology Center, Mansoura University, Mansoura, Egypt. ezzelgamal_1962@yahoo.com

RESUMEN / SUMMARY: - **BACKGROUND:** While current pathological and clinical parameters provide important prognostic information, they still have a limited ability to predict the true malignant potential of most bladder tumors. Therefore, the present study was carried out to investigate the levels of anti-apoptotic proteins such as p53 and Bcl-2, and of apoptosis itself as reflected by the increase in sub-G1 peak staining, in the blood and urine of bladder cancer patients, and to thus determine the usefulness of these parameters as tools for early and accurate prediction of tumor growth and development of metastases, in order to assess treatment benefit potential. **METHODS:** A total of 80 bladder cancer patients and 50 healthy controls without malignancies were enrolled in this study. The levels of p53, Bcl-2 and apoptosis (sub-G1 peak) were evaluated by flow cytometry in the urine and blood of patients and controls. **RESULTS:** Levels of p53, Bcl-2 and apoptosis were significantly higher in the urine sediment than in the blood. Moreover, p53 levels in the blood and urine of bladder cancer patients were significantly higher than in controls, and were significantly increased during the development of tumor grades and in association with positive parameters of urine analysis. In contrast, Bcl-2 and apoptosis levels in the blood and urine of bladder cancer patients were significantly lower than in samples from controls, and were significantly decreased during the development of tumor grades and in association with positive parameters of urine analysis. Apoptosis levels were positively correlated with Bcl-2 levels but negatively correlated with p53 levels. **CONCLUSIONS:** These findings suggest that quantitative analysis of p53, Bcl-2 and apoptosis, especially in the urine sediment, may be a useful tool in the diagnosis of bladder cancer.

[686]

TÍTULO / TITLE: - Human umbilical cord blood-derived stromal cells: A new resource for the proliferation and apoptosis of myeloma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hematology. 2013 Jul 27.

- Enlace al texto completo (gratis o de pago)

[1179/1607845413Y.0000000107](https://doi.org/10.1179/1607845413Y.0000000107)

AUTORES / AUTHORS: - Gao L; Zhang C; Zhang X; Gao L; Hao L; Chen XH

RESUMEN / SUMMARY: - Background/Objective: Bone marrow stromal cells (BMSCs) can support multiple myeloma (MM) disease progression and resistance to chemotherapy. The proliferation of MM cells may be suppressed by modifying the hematopoietic microenvironment (HME). We have previously isolated human umbilical cord blood-derived stromal cells (hUCBDSCs) and observed that hUCBDSCs suppressed proliferation and induced apoptosis in KM3 cells. To examine the mechanism by which hUCBDSCs drive the inhibition of MM, KM3 cells were co-cultured with hUCBDSCs. METHODS: Interleukin (IL)-6 and soluble IL-6 receptor (sIL-6R) expression levels were measured by enzyme-linked immunosorbent assay. The expression levels of membrane IL-6 receptor (mIL-6R), intercellular cell adhesion molecule-1 (ICAM-1), B-cell lymphoma/leukemia-2 (Bcl-2), and Bcl-XL as well as the location of nuclear factor kappaB (NF-kappaB) were assessed by laser confocal microscopy. The expression profiles of mIL-6R and ICAM-1 were also more precisely examined by flow cytometry, and Bcl-2, Bcl-XL and inhibitor kappa B expression levels were analyzed by western blot. The mRNA expression levels of IL-6R, ICAM-1, Bcl-2, and Bcl-XL were assessed by real-time polymerase chain reaction. NF-kappaB DNA-binding activity was examined by electrophoretic mobility shift assay. RESULTS: The protein expression levels of both sIL-6R and mIL-6R were reduced in culture conditions when KM3 cells were co-cultured with hUCBDSCs; moreover, the mRNA expression levels of IL-6R were also reduced. Nuclear translocation of the NF-kappaB p65 subunit was inhibited in KM3 cells by co-culture with hUCBDSCs. Moreover, hUCBDSCs inhibited NF-kappaB DNA-binding activity, thereby resulting in the downregulation of NF-kappaB-regulated proteins. CONCLUSION: hUCBDSCs can suppress proliferation and induce apoptosis in KM3 cells by both downregulating IL-6R expression and inhibiting NF-kappaB activity.

[687]

TÍTULO / TITLE: - Acupuncture for treatment of arthralgia secondary to aromatase inhibitor therapy in women with early breast cancer: pilot study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acupunct Med. 2013 May 30.

●● Enlace al texto completo (gratis o de pago) [1136/acupmed-2012-010309](https://doi.org/10.1179/1607845413Y.0000000107)

AUTORES / AUTHORS: - Oh B; Kimble B; Costa DS; Davis E; McLean A; Orme K; Beith J

INSTITUCIÓN / INSTITUTION: - Sydney Medical School, University of Sydney, , Sydney, New South Wales, Australia.

RESUMEN / SUMMARY: - BACKGROUND: Aromatase inhibitors (AIs) are recommended as adjuvant hormone treatment for postmenopausal women with early breast cancer. A substantial proportion of women taking AIs experience joint pain and stiffness. Studies have suggested that acupuncture may be effective in treating joint pain. OBJECTIVE: A pilot study was conducted to evaluate the feasibility, safety and efficacy of using acupuncture to treat AI-induced arthralgia. METHODS: A total of 32 patients were randomised to receive either sham or real electroacupuncture (EA) twice weekly for 6 weeks. Outcomes of joint pain, stiffness and physical function were measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), overall pain severity and interference with the BPI-SF and quality of life (QOL) with the Functional Assessment of Cancer Therapy-General (FACT-G) instrument. Hand strength was assessed by a grip test, and a serum marker of inflammation (C reactive protein (CRP)) was also measured. All assessments were performed at baseline, 6 weeks and 12 weeks, except for blood samples at baseline and 6 weeks only. RESULTS: No serious adverse events were reported during or after acupuncture treatments. There were no significant differences in outcome measures. However, positive trends were observed in stiffness and physical function at week 12 in favour of real EA. CONCLUSIONS: Findings suggest that acupuncture is feasible and safe in patients with breast cancer with joint pain caused by AI. A larger study with adequately powered to confirm these results and detect clinically relevant effects is needed.

[688]

TÍTULO / TITLE: - Advances in the treatment of metastatic prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Practitioner. 2013 Apr;257(1760):15-8, 2.

AUTORES / AUTHORS: - Chowdhury S; Kirby R

INSTITUCIÓN / INSTITUTION: - The Prostate Centre, London, UK.

RESUMEN / SUMMARY: - Prostate cancer is the most common cancer in men in the UK. It accounts for nearly a quarter of all male cancer diagnoses and is the second most common cause of male cancer death. Despite a large increase in prostate cancer incidence, mortality rates have remained relatively constant through improvements in survival. Most patients present with localised disease, but there are still many who present with metastatic disease. Prostate cancers are driven by androgens, such as testosterone. Androgen deprivation therapy (ADT), which is still the mainstay of systemic treatment, effectively reduces intraprostatic androgen levels resulting in reduced androgen receptor (AR) stimulation and increased apoptosis. Medical castration using LHRH analogues has become the gold standard in managing both locally advanced prostate cancer, in combination with radiotherapy, and metastatic disease. Eventually most men with advanced prostate cancer become resistant to ADT. This is now called castrate refractory prostate cancer (CRPC), and is associated with a poor

prognosis. There is now hope for patients who progress after chemotherapy with the emergence of several new agents that have been shown to benefit patients. The first AR-targeted drug to show a definite clinical benefit is abiraterone. It markedly decreases levels of androgens in CRPC and initial trials showed promising activity. Enzalutamide has a high affinity and selectivity for AR binding, blocks nuclear translocation and reduces recruitment of co-activators. Abiraterone, enzalutamide and other AR-targeted drugs are being studied in clinical trials for patients earlier in their disease, e.g. in addition to ADT at first presentation of metastatic disease, where it is likely that greater benefits will be seen.

[689]

TÍTULO / TITLE: - Pharmacogenomics Variation in Drug Metabolizing Enzymes and Transporters in Relation to Docetaxel Toxicity in Lebanese Breast Cancer Patients: Paving the Way for OMICS in Low and Middle Income Countries.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - OMICS. 2013 Jul;17(7):353-67. doi: 10.1089/omi.2013.0019. Epub 2013 Jun 11.

●● [Enlace al texto completo \(gratis o de pago\) 1089/omi.2013.0019](#)

AUTORES / AUTHORS: - Awada Z; Haider S; Tfayli A; Bazarbachi A; El-Saghir NS; Salem Z; Shamseddine A; Taher A; Zgheib NK

INSTITUCIÓN / INSTITUTION: - 1 Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut , Beirut, Lebanon .

RESUMEN / SUMMARY: - Abstract We investigated the association of genetic polymorphisms in drug metabolizing enzymes (DMEs) and transporters in patients with docetaxel-induced febrile neutropenia, by a new high-throughput DMEs and transporters (DMETPlus) microarray platform, characterizing 1936 single nucleotide polymorphisms (SNPs) in 225 genes. We recruited 100 Lebanese breast cancer patients from a consecutive cohort of 277 patients who received docetaxel either alone, or in combination with trastuzumab. Out of 100 patients, 18 had developed febrile neutropenia (cases). They were age- and treatment- matched with 18 patients who did not develop febrile neutropenia on docetaxel (controls). We found that 12 SNPs in seven genes (ABCC6, ABCG1, ABCG2, CYP1A2, CYP2D6, FMO2, and FMO3) were significantly associated with febrile neutropenia after docetaxel treatment. Many of these SNPs have not been previously reported to be associated with toxicity due to docetaxel treatment. Interestingly, one SNP in the FMO3 gene (rs909530) was significantly associated with three clinical endpoints: febrile neutropenia, reduced absolute neutrophil count, and hemoglobin reduction. To the best of our knowledge, this is the first study that evaluated the effect of a large array of nearly 2000 polymorphisms in DMEs and transporters on docetaxel toxicity in breast cancer patients, and in a previously understudied population. Additionally, it attests to the feasibility of genomics research in low- and middle-

income countries (LMICs). In light of the current global epidemic of noncommunicable diseases (NCDs) such as breast cancer impacting LMICs, we suggest pharmacogenomics is considered as an integral part of the global health research agenda for NCDs and personalized therapeutics.

[690]

TÍTULO / TITLE: - Prognostic implication of BAALC gene expression in adult acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lab. 2013;59(5-6):621-8.

AUTORES / AUTHORS: - Yahya RS; Sofan MA; Abdelmasseih HM; Saady N; Sharaf-Eldein MA

INSTITUCIÓN / INSTITUTION: - Children Hospital, Faculty of Medicine, Mansoura University, Mansoura, Egypt. yahyaraida@hotmail.com

RESUMEN / SUMMARY: - BACKGROUND: Recently various molecular markers and global gene expression profiling have been investigated to improve risk profile characterization of AML with normal cytogenetics. Our main objective is to investigate the prognostic impact of brain and acute leukemia, cytoplasmic (BAALC) expression in AML with normal karyotype. METHODS: BAALC expression was analysed using quantitative real time (QRT) PCR. RESULTS: High expression was detected in 22 of 45 patients (48.9%) and its expression did not correlate with the clinical parameters of patients. High BAALC expressers had significantly lower incidence of CR (22.7% vs. 73.9%; $p = 0.001$), higher mortality rate (72.1% vs. 39.1%; $p = 0.023$), showed significantly shorter DFS (mean 4.5 vs. 13.21 months, $p < 0.001$), and inferior overall survival (7.02 vs. 15.02 months, $p < 0.001$). Multivariable analysis confirmed high BAALC expression as an independent risk factor for DFS and OS. CONCLUSIONS: BAALC expression is an important prognostic factor in AML patients with normal karyotype and its incorporation into novel risk-adapted therapeutic strategies will improve the currently disappointing cure rate of this group of patients.

[691]

TÍTULO / TITLE: - Prognostic value of phosphorylated HER2 in HER2-positive breast cancer patients treated with adjuvant trastuzumab.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Breast Cancer. 2013 Jun 8.

●● Enlace al texto completo (gratis o de pago) [1007/s12282-013-0478-](http://1007/s12282-013-0478-4)

[Y](#)

AUTORES / AUTHORS: - Kurebayashi J; Kanomata N; Yamashita T; Shimo T; Mizutoh A; Moriya T; Sonoo H

INSTITUCIÓN / INSTITUTION: - Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama, 701-0192, Japan, kure@med.kawasaki-m.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: Adjuvant trastuzumab has been routinely used in HER2-positive operable breast cancer patients. Prognostic factors remain to be well characterized in these patients and might correlate with primary and/or acquired resistance to trastuzumab. PATIENTS AND METHODS: The study subjects were 78 HER2-positive operable breast cancer patients treated with adjuvant chemotherapy followed by 1-year trastuzumab between 2005 and 2010 in our institute. All breast tumors showed a HercepTest score of 3+ or that of 2+ and positive fluorescence in situ hybridization. Expression levels of HER1, phosphorylated HER2 (pY1248), HER3, HER4, and p53 were assessed by immunohistochemistry. Prognostic factors were investigated with univariate and multivariate analyses using the Kaplan-Meier/log-rank test and Cox proportional hazards model, respectively. RESULTS: The median age and follow-up period of the patients were 54 years and 39 months, respectively. The mean tumor size was 2.1 cm and the node-positive rate was 42 %. Eight patients had recurrent diseases but no patient died of cancer. Univariate analysis revealed that pHER2 positivity was only a significantly worse prognostic factor for relapse-free survival (RFS) ($P = 0.049$). A HercepTest score of 2+ and high expression level of p53 showed a trend. Multivariate analysis revealed three biological markers: pHER2 positivity [hazard ratio (HR) = 11.6, 95 % confidence interval (CI) 1.3-111.1, $P = 0.031$], p53 positivity (HR = 6.4, 95 % CI 1.0-40.0, $P = 0.047$) and a HercepTest score of 2+ (HR = 8.6, 95 % CI 1.6-45.2, $P = 0.011$) to be worse prognostic factors for RFS. Notably, three out of five patients with breast tumors expressing HER2 at a score of 2+ and pHER2 had recurrent diseases. Interestingly, the expression level of pHER2 significantly correlated with the expression levels of HER2 and HER3 in HER2-positive breast tumors. CONCLUSIONS: This retrospective cohort study suggests that a lower expression level of HER2 and high expression levels of pHER2 and p53 may indicate a worse prognosis in HER2-positive breast cancer patients treated with trastuzumab and chemotherapy. Further studies are needed to evaluate pHER2 expression in HER2-positive breast cancer as a prognostic and/or predictive marker.

[692]

TÍTULO / TITLE: - Perceived Versus Predicted Risks of Colorectal Cancer and Self-Reported Colonoscopies by Members of Mismatch Repair Gene Mutation-Carrying Families Who Have Declined Genetic Testing.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Genet Couns. 2013 Jun 9.

●● Enlace al texto completo (gratis o de pago) [1007/s10897-013-9614-](#)

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AUTORES / AUTHORS: - Flander L; Speirs-Bridge A; Rutstein A; Niven H; Win AK; Ait Ouakrim D; Hopper JL; Macrae F; Keogh L; Gaff C; Jenkins M

INSTITUCIÓN / INSTITUTION: - Centre for Molecular, Environmental, Genetic & Analytic Epidemiology, The University of Melbourne, Melbourne, VIC, 3010, Australia, l.flander@unimelb.edu.au.

RESUMEN / SUMMARY: - People carrying germline mutations in mismatch repair genes are at high risk of colorectal cancer (CRC), yet about half of people from mutation-carrying families decline genetic counselling and/or testing to identify mutation status. We studied the association of quantitative measures of risk perception, risk prediction and self-reported screening colonoscopy in this elusive yet high-risk group. The sample of 26 participants (mean age 43.1 years, 14 women) in the Australasian Colorectal Cancer Family Registry were relatives of mutation carriers; had not been diagnosed with any cancer at the time of recruitment and had declined an invitation to attend genetic counselling and/or testing. A structured elicitation protocol captured perceived CRC risk over the next 10 years. Self-reported colonoscopy screening was elicited during a 45-minute semi-structured interview. Predicted 10-year CRC risk based on age, gender, known mutation status and family history was calculated using "MMRpro." Mean perceived 10-year risk of CRC was 31 % [95 % CI 21, 40], compared with mean predicted risk of 4 % [2, 7] ($p < 0.001$); this was independent of age and sex ($p = 0.9$). Among those reporting any medical advice and any screening colonoscopy ($n = 18$), those with higher risk perception had less frequent colonoscopy (Pearson's $r = 0.49$ [0.02, 0.79]). People who decline genetic testing for CRC susceptibility mutations perceive themselves to be at substantially higher risk than they really are. Those with high perceived risk do not undertake screening colonoscopy more often than those who perceive themselves to be at average risk.

[693]

TÍTULO / TITLE: - Plasma Levels of Phospholipase A-IIA in Patients with Different Types of Malignancies: Prognosis and Association with Inflammatory and Coagulation Biomarkers.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Jun 1.

- Enlace al texto completo (gratis o de pago) [1007/s12253-013-9652-](#)

[v](#)

AUTORES / AUTHORS: - Menschikowski M; Hagelgans A; Schuler U; Froeschke S; Rosner A; Siegert G

INSTITUCIÓN / INSTITUTION: - Institut für Klinische Chemie und Laboratoriumsmedizin, Medizinische Fakultät "Carl Gustav Carus", Technische Universität Dresden, Fetscherstrasse 74, 01307, Dresden, Germany, Mario.Menschikowski@uniklinikum-dresden.de.

RESUMEN / SUMMARY: - It is well-known that the plasma level of group IIA phospholipase A2 (sPLA2-IIA) is increased in patients with malignant diseases, but whether the up-regulated enzyme expression is directly related to tumorigenesis or a consequence of tumor-associated inflammation remains unresolved. In this study we analyzed circulating levels of sPLA2-IIA, C-reactive protein (CRP), fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), and antithrombin as biomarkers of inflammation and coagulation in patients with various types of malignancies. Underlying tumor entities were lung, esophageal, gastric, pancreatic, colorectal, head and neck, and hepatocellular carcinomas as well as multiple myeloma and non-Hodgkin's lymphoma. Plasma levels of sPLA2-IIA are shown to be markedly increased in all types of analysed malignancies in comparison to the normal range (22.8 +/- 4.5 mug/L versus <1.9 mug/L). Levels of sPLA2-IIA correlate positively with CRP ($p < 0.001$), fibrinogen ($p < 0.01$), FVIII ($p < 0.05$), and vWF ($p < 0.05$) and negatively with antithrombin levels ($p < 0.05$). Kaplan-Meier analyses revealed a statistically prolonged survival time of patients with lower sPLA2-IIA concentrations (<4 mug/L) in comparison to those with elevated concentrations (>4 mug/L) of this enzyme. In conclusion, the study shows that the measurement of plasma sPLA2-IIA levels has prognostic values in patients with different types of malignancies. The association of sPLA2-IIA levels with CRP, fibrinogen, FVIII, and vWF levels supports the importance of inflammatory processes for the up-regulation of sPLA2-IIA during cancer progression.

[694]

TÍTULO / TITLE: - Determination of EGFR mutations in single cells microdissected from enriched lung tumor cells in peripheral blood.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Anal Bioanal Chem. 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1007/s00216-013-7156-](#)

[y](#)

AUTORES / AUTHORS: - Ran R; Li L; Wang M; Wang S; Zheng Z; Lin PP

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, 100730, China.

RESUMEN / SUMMARY: - A minimally invasive and repeatable approach for real-time epidermal growth factor receptor (EGFR) mutation surveillance would be highly beneficial for individualized therapy of late stage lung cancer patients whose surgical specimens are often not available. We aim to develop a viable method to detect EGFR mutations in single circulating tumor cells (CTCs). Using a model CTC system of spiked tumor cells in whole blood, we evaluated EGFR mutation determination in single tumor cells enriched from blood. We used magnetic beads labeled with antibody against leukocyte surface antigens to deplete leukocytes and enrich native CTCs independent of epithelial marker

expression level. We then used laser cell microdissection (LCM) to isolate individual CTCs, followed by whole-genome amplification of the DNA for exon 19 microdeletion, L858R and T790M mutation detection by PCR sequencing. EGFR mutations were successfully measured in individual spiked tumor cells enriched from 7.5 ml whole blood. Whole-genome amplification provided sufficient DNA for mutation determination at multiple sites. Ninety-five percent of the single CTCs microdissected by LCM (19/20) yielded PCR amplicons for at least one of the three mutation sites. The amplification success rates were 55 % (11/20) for exon 19 deletion, 45 % (9/20) for T790M, and 85 % (17/20) for L858R. Sequencing of the amplicons showed allele dropout in the amplification reactions, but mutations were correctly identified in 80 % of the amplicons. EGFR mutation determination from single captured tumor cells from blood is feasible with the approach described here. However, to overcome allele dropout and to obtain reliable information about the tumor's EGFR status, multiple individual tumor cells should be assayed.

[695]

TÍTULO / TITLE: - Synergistic induction of apoptosis in multiple myeloma cells by bortezomib and hypoxia-activated prodrug TH-302, in vivo and in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jul 5.

- [Enlace al texto completo \(gratis o de pago\) 1158/1535-7163.MCT-13-0123](#)

AUTORES / AUTHORS: - Hu J; Van Valckenborgh E; Dehui X; Menu E; De Raeve H; De Bruyne E; Xu S; Van Camp B; Handisides D; Hart CP; Vanderkerken K

INSTITUCIÓN / INSTITUTION: - 1Department of Genetics and Molecular Biology, Xi'an Jiaotong University School of Medicine.

RESUMEN / SUMMARY: - Recently, we demonstrated that hypoxia is a critical microenvironmental factor in multiple myeloma (MM), and that the hypoxia-activated prodrug TH-302 selectively targets hypoxic MM cells and improves multiple disease parameters in vivo. To explore approaches for sensitizing MM cells to TH-302, we evaluated in this study the anti-tumor effect of TH-302 in combination with the clinically used proteasome inhibitor bortezomib. First, we show that TH-302 and bortezomib synergistically induce apoptosis in MM cell lines in vitro. Second, we confirm that this synergism is related to the activation of caspase cascades and is mediated by changes of Bcl-2 family proteins. The combination treatment induces enhanced cleavage of caspase-3/8/9 and PARP, and therefore triggers apoptosis and enhances the cleavage of pro-apoptotic BH3-only protein BAD and BID as well as the anti-apoptotic protein Mcl-1. In particular, TH-302 can abrogate the accumulation of anti-apoptotic Mcl-1 induced by bortezomib, and decreases the expression of the pro-survival proteins Bcl-2 and Bcl-xL. Furthermore, we found that the induction of the pro-apoptotic BH3-only proteins PUMA and NOXA is associated with this

synergism. In response to the genotoxic and ER stresses by TH-302 and bortezomib, the expression of PUMA and NOXA were up-regulated in p53-dependent and p53-independent manners. Finally, in the murine 5T33MMv model, we demonstrated that the combination of TH-302 and bortezomib can improve multiple disease parameters and significantly prolong the survival of diseased mice. In conclusion, our studies provide a rationale for clinical evaluation of the combination of TH-302 and bortezomib in MM patients.

[696]

TÍTULO / TITLE: - Association of ABCB1 genetic polymorphisms with susceptibility to colorectal cancer and therapeutic prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Jun;14(8):897-911. doi: 10.2217/pgs.13.78.

●● [Enlace al texto completo \(gratis o de pago\) 2217/pgs.13.78](#)

AUTORES / AUTHORS: - Wu H; Kang H; Liu Y; Xiao Q; Zhang Y; Sun M; Liu D; Wang Z; Zhao H; Yao W; Jia T; Wang E; Zheng Z; Wei M

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, School of Pharmaceutical Sciences, China Medical University, Shenyang, Liaoning Province 110001, People's Republic of China.

RESUMEN / SUMMARY: - AIM: To evaluate the association of ABCB1 gene polymorphisms with susceptibility to colorectal cancer (CRC) and clinical outcomes of CRC patients with chemotherapy. PATIENTS & METHODS: A case-control study was performed on the C3435T, C1236T and G2677T/A polymorphisms in the ABCB1 gene in 1028 CRC patients and 1230 controls. RESULTS: We observed that the ABCB1 C3435T and G2677T/A variants as well as the 3435T-1236T-2677T haplotype significantly increased the risk of CRC. The ABCB1 C3435T CT genotype had a significant effect on the time to recurrence (adjusted hazard ratio [HR; 95% CI]: 0.560 [0.355-0.882]; p = 0.012). Moreover, ABCB1 C1236T variant carriers displayed a longer overall survival after postoperative oxaliplatin-based chemotherapy (adjusted HR [95% CI]: 0.354 [0.182-0.692], 0.646 [0.458-0.910], respectively). In addition, 1236TT-2677TT-3435TT haplotype carriers showed a worse progression-free survival (adjusted HR [95% CI]: 1.477 [1.012-3.802]; p = 0.043) and recurrence-free survival (adjusted HR [95% CI]: 2.183 [1.253-3.802]; p = 0.006). CONCLUSION: The ABCB1 polymorphisms might be a candidate pharmacogenomic factor to assess susceptibility and prognosis after oxaliplatin-based chemotherapy for CRC patients.

[697]

TÍTULO / TITLE: - Maytenus ilicifolia dry extract protects normal cells, induces apoptosis and regulates Bcl-2 in human cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Exp Biol Med (Maywood). 2013 Jul 4.

●● Enlace al texto completo (gratis o de pago)

[1177/1535370213494563](#)

AUTORES / AUTHORS: - Junior RF; Oliveira AL; Pessoa JB; Garcia VB; Guerra GC; Soares LA; de Souza TP; Petrovick PR; de Araujo AA

INSTITUCIÓN / INSTITUTION: - Department of Morphology, Federal University of Rio Grande do Norte, Natal, Cep: 59078-970, Brazil.

RESUMEN / SUMMARY: - Maytenus is the largest genus of the family Celastraceae and the species Maytenus ilicifolia (popularly known as 'Espinheira Santa'). It is widely used in traditional Brazilian medicine to treat stomach conditions including nausea, gastritis, and ulcers. In this study, the apoptotic effects of a spray-dried extract of M. ilicifolia (SDEMI) was evaluated using human hepatocellular cells (HepG2), colorectal carcinoma cells (HT-29), and normal keratinocytes (HaCaT). Cells were treated with SDEMI for 4 and 24 h, then were assayed for levels of apoptosis, caspase-3, and Bcl-2 by flow cytometry, immunostaining, and Western blot, respectively. Significant differences between groups were determined using analysis of variance ($P < 0.05$). For HepG2 and HT-29 cells treated with SDEMI, various cytotoxic effects were observed compared with control cells at all timepoints assayed ($P < 0.001$). Furthermore, positive caspase-3 staining and down-regulation of Bcl-2 were observed, consistent with the induction of cell death detected in these cell lines. In contrast, treatment of HaCaT cells with SDEMI was associated with a protective effect compared with control cells at both timepoints ($P < 0.001$). For example, increased expression of Bcl-2 and negative caspase-3 staining were detected. Taken together, these results suggest that SDEMI protects normal cells, while SDEMI mediates induction of apoptosis via down-regulation of Bcl-2 and involvement of caspase-3 in human carcinoma cells.

[698]

TÍTULO / TITLE: - Biochemical changes accompanying apoptotic cell death in retinoblastoma cancer cells treated with lipogenic enzyme inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Jun 29;1831(9):1458-1466. doi: 10.1016/j.bbali.2013.06.005.

●● Enlace al texto completo (gratis o de pago)

[1016/j.bbali.2013.06.005](#)

AUTORES / AUTHORS: - Vandhana S; Coral K; Jayanthi U; Deepa PR; Krishnakumar S

INSTITUCIÓN / INSTITUTION: - Dept. of Ocular Pathology, Vision Research Foundation, Sankara Nethralaya, Chennai, India; Dept. of Biological Sciences, Birla Institute of Technology & Science (BITS), Pilani, Rajasthan, India.

RESUMEN / SUMMARY: - Retinoblastoma (RB) is a malignant intra-ocular neoplasm that affects children (usually below the age of 5years). In addition to conventional chemotherapy, novel therapeutic strategies that target metabolic pathways such as glycolysis and lipid metabolism are emerging. Fatty acid synthase (FASN), a lipogenic multi-enzyme complex, is over-expressed in retinoblastoma cancer. The present study evaluated the biochemical basis of FASN inhibition induced apoptosis in cultured Y79 RB cells. FASN inhibitors (cerulenin, triclosan and orlistat) significantly inhibited FASN enzyme activity ($P < 0.05$) in Y79 RB cells. This was accompanied by a decrease in palmitate synthesis (end-product depletion), and increased malonyl CoA levels (substrate accumulation). Differential lipid profile was biochemically estimated in neoplastic (Y79 RB) and non-neoplastic (3T3) cells subjected to FASN inhibition. The relative proportion of phosphatidyl choline to neutral lipids (triglyceride+total cholesterol) in Y79 RB cancer cells was found to be higher than the non-neoplastic cells, indicative of altered lipid distribution and utilization in tumor cells. FASN inhibitor treated Y79 RB and fibroblast cells showed decrease in the cellular lipids (triglyceride, cholesterol and phosphatidyl choline) levels. Apoptotic DNA damage induced by FASN inhibitors was accompanied by enhanced lipid peroxidation.

[699]

TÍTULO / TITLE: - Histone deacetylase inhibitors modulate miRNA and mRNA expression, block metaphase, and induce apoptosis in inflammatory breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jul 1;14(7):658-71. doi: 10.4161/cbt.25088. Epub 2013 Jun 24.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.25088](#)

AUTORES / AUTHORS: - Chatterjee N; Wang WL; Conklin T; Chittur S; Tenniswood M

INSTITUCIÓN / INSTITUTION: - Cancer Research Center; Department of Biomedical Sciences; School of Public Health; University at Albany; Rensselaer, NY USA.

RESUMEN / SUMMARY: - To develop new therapies for inflammatory breast cancer (IBC) we have compared the effects of two hydroxamic acid-based histone deacetylase (HDAC) inhibitors, CG-1521 and Trichostatin A (TSA) on the biology of two IBC cell lines: SUM149PT and SUM190PT. CG-1521 and TSA induce dose (0-10 microM) and time-dependent (0-96 h) increases in the proportion of cells undergoing cell cycle arrest and apoptosis in the presence or absence of 17beta-estradiol. In SUM 149PT cells, both CG-1521 and TSA increase the levels of acetylated alpha-tubulin; however the morphological effects are different: CG-1521 blocks mitotic spindle formation and prevents abscission during cytokinesis while TSA results in an increase in cell size. In

SUM190PT cells CG-1521 does not cause an increase in acetylated-alpha-tubulin and even though TSA significantly increases the levels of acetylated tubulin, neither inhibitor alters the morphology of the cells. Microarray analysis demonstrates that CG-1521 modulates the expression of 876 mRNAs and 63 miRNAs in SUM149PT cells, and 1227 mRNAs and 35 miRNAs in SUM190PT cells. Only 9% of the genes are commonly modulated in both cell lines, suggesting that CG-1521 and TSA target different biological processes in the two cell lines most likely though the inhibition of different HDACs in these cell lines. Gene ontology (GO) analysis reveals that CG-1521 affects the expression of mRNAs that encode proteins associated with the spindle assembly checkpoint, chromosome segregation, and microtubule-based processes in both cell lines and has cell-type specific effects on lipid biosynthesis, response to DNA damage, and cell death.

[700]

TÍTULO / TITLE: - Systemic inflammatory status at baseline predicts bevacizumab benefit in advanced non-small cell lung cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun;14(6):469-75. doi: 10.4161/cbt.24425.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.24425](#)

AUTORES / AUTHORS: - Botta C; Barbieri V; Ciliberto D; Rossi A; Rocco D; Addeo R; Staropoli N; Pastina P; Marvaso G; Martellucci I; Guglielmo A; Pirtoli L; Sperlongano P; Gridelli C; Caraglia M; Tassone P; Tagliaferri P; Correale P

INSTITUCIÓN / INSTITUTION: - Medical Oncology Unit, Campus Salvatore Venuta, Department of Experimental and Clinical Medicine, Magna Graecia University and Tommaso Campanella Cancer Center, Catanzaro, Italy.

RESUMEN / SUMMARY: - Bevacizumab is a humanized anti-VEGF monoclonal antibody able to produce clinical benefit in advanced non-squamous non-small-cell lung cancer (NSCLC) patients when combined to chemotherapy. At present, while there is a rising attention to bevacizumab-related adverse events and costs, no clinical or biological markers have been identified and validated for baseline patient selection. Preclinical findings suggest an important role for myeloid-derived inflammatory cells, such as neutrophils and monocytes, in the development of VEGF-independent angiogenesis. We conducted a retrospective analysis to investigate the role of peripheral blood cells count and of an inflammatory index, the neutrophil-to-lymphocyte ratio (NLR), as predictors of clinical outcome in NSCLC patients treated with bevacizumab plus chemotherapy. One hundred and twelve NSCLC patients treated with chemotherapy +/- bevacizumab were retrospectively evaluated for the predictive value of clinical or laboratory parameters correlated with inflammatory status. Univariate analysis revealed that a high number of circulating neutrophils and monocytes as well as a high NLR were associated with shorter

progression-free survival (PFS) and overall survival (OS) in bevacizumab-treated patients only. We have thus developed a model based on the absence or the presence of at least one of the above-mentioned inflammatory parameters. We found that the absence of all variables strongly correlated with longer PFS and OS (9.0 vs. 7.0 mo, HR: 0.39, $p = 0.002$; and 20.0 vs. 12.0 mo, HR: 0.29, $p < 0.001$ respectively) only in NSCLC patients treated with bevacizumab plus chemotherapy. Our results suggest that a baseline systemic inflammatory status is marker of resistance to bevacizumab treatment in NSCLC patients.

[701]

TÍTULO / TITLE: - Effect of doxorubicin, oxaliplatin, and methotrexate administration on the transcriptional activity of BCL-2 family gene members in stomach cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jul 1;14(7):587-96. doi: 10.4161/cbt.24591. Epub 2013 May 10.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.24591](#)

AUTORES / AUTHORS: - Florou D; Patsis C; Ardavanis A; Scorilas A

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology; Faculty of Biology; University of Athens; Athens, Greece.

RESUMEN / SUMMARY: - Defective apoptosis comprises the main reason for tumor aggressiveness and chemotherapy tolerance in solid neoplasias. Among the BCL-2 family members, whose mRNA or protein expression varies considerably in different human malignancies, BCL2L12 is the one for which we have recently shown its propitious prognostic value in gastric cancer. The purpose of the current work was to investigate the expression behavior of BCL2L12, BAX, and BCL-2 in human stomach adenocarcinoma cells following their exposure to anti-tumor substances. The 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide and trypan blue methods assessed the impact of doxorubicin, oxaliplatin and methotrexate on AGS cells' viability and growth. Following isolation from cells, total RNA was reverse-transcribed to cDNA. Quantification of target genes' expression was performed with real-time PCR using SYBR Green detection system. The relative changes in their mRNA levels between drug-exposed and untreated cells were calculated with the comparative Ct method ($2^{-\Delta\Delta Ct}$). All three drugs, as a result of their administration to AGS cancer cells for particular time intervals, provoked substantial fluctuations in the transcriptional levels of the apoptosis-related genes studied. While BAX was principally upregulated, striking similar were the notable changes regarding BCL-2 and BCL2L12 expression in our cellular system. Our findings indicate the growth suppressive effects of doxorubicin, oxaliplatin and methotrexate treatment on stomach carcinoma cells and the

implication of BCL2L12, BAX, and BCL-2 expression profiles in the molecular signaling pathways triggered by chemotherapy.

[702]

TÍTULO / TITLE: - Spindle assembly checkpoint gene expression in childhood adrenocortical tumors (ACT): Overexpression of Aurora kinases A and B is associated with a poor prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Pediatr Blood Cancer*. 2013 Jun 20. doi: 10.1002/pbc.24653.

●● [Enlace al texto completo \(gratis o de pago\) 1002/pbc.24653](#)

AUTORES / AUTHORS: - Borges KS; Moreno DA; Martinelli CE Jr; Antonini SR; de Castro M; Tucci S Jr; Neder L; Ramalho LN; Seidinger AL; Cardinali I; Mastellaro MJ; Yunes JA; Brandalise SR; Tone LG; Scrideli CA

INSTITUCIÓN / INSTITUTION: - Department of Genetics, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - BACKGROUND: Pediatric adrenocortical tumors (ACT) are rare malignancies and treatment has a small impact on survival in advanced disease and the discovery of potential target genes could be important in new therapeutic approaches. METHODS: The mRNA expression levels of spindle checkpoint genes AURKA, AURKB, BUB, and BUBR1 were analyzed in 60 children with ACT by quantitative real time PCR. The anticancer effect of ZM447439, an experimental AURK inhibitor, was analyzed in a primary childhood ACT culture carrying the TP53 p.R337H mutation. RESULTS: A significant association was observed between malignancy as defined by Weiss score ≥ 3 and higher AURKA (2.0-fold, $P = 0.01$), AURKB (7.0-fold, $P = 0.007$), and BUBR1 (5.8-fold, $P = 0.007$) gene expression, and between unfavorable event (death or relapse) and higher expression of AURKA (6.0-fold, $P = 0.034$) and AURKB (17-fold, $P = 0.013$). Overexpression of AURKA and AURKB was associated with lower event-free survival in uni- ($P < 0.001$ and $P = 0.006$, respectively) and multivariate ($P = 0.002$ and $P = 0.03$, respectively) analysis. Significant lower Event free survival (EFS) was also observed in patients with moderate/strong immunostaining to AURKA ($P = 0.012$) and AURKB ($P = 0.045$). ZM447439 was able to induce inhibition of proliferation and colony formation in a primary childhood ACT culture carrying the TP53 p.R337H mutation. CONCLUSION: Our results suggest that AURKA and AURKB overexpression in pediatric ACT may be related to more aggressive disease and the inhibition of these proteins could be an interesting approach for the treatment of these tumors. *Pediatr Blood Cancer*. © 2013 Wiley Periodicals, Inc.

[703]

TÍTULO / TITLE: - Metallothionein 2^a inhibits NF-kappaB pathway activation and predicts clinical outcome segregated with TNM stage in gastric cancer patients following radical resection.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Transl Med. 2013 Jul 19;11:173. doi: 10.1186/1479-5876-11-173.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-173](#)

AUTORES / AUTHORS: - Pan Y; Huang J; Xing R; Yin X; Cui J; Li W; Yu J; Lu Y

INSTITUCIÓN / INSTITUTION: - Laboratory of Molecular Oncology, Key laboratory of Carcinogenesis and Translational Research, Ministry of Education, Peking University Cancer Hospital & Institute, No.52 Fucheng Road, Beijing, Haidian District 100142, PR China.

RESUMEN / SUMMARY: - BACKGROUND: Metallothionein 2^a (MT2A) as a stress protein, plays a protective role in gastric mucosal barrier. Its role in the development of gastric cancer (GC) is unclear. The mechanism of MT2A will be investigated in gastric tumorigenesis. METHODS: MT2A expression was detected in 973 gastric specimens. The biological function was determined through ectopic expressing MT2A in vitro and in vivo. The possible downstream effectors of MT2A were investigated in NF-kappaB signaling. The protein levels of MT2A, I kappa B-alpha and p-I kappa B-alpha (ser32/36) expression were analyzed in a subset of 258 patients by IHC staining. The prognostic effects of MT2A, status of I kappa B-alpha and TNM stage were evaluated using the Kaplan-Meier method and compared using the log-rank test. RESULTS: Decreased MT2A expression was detected in cell lines and primary tumors of GC. In clinical data, loss of MT2A (MT2A + in Normal (n =171, 76.0%); Intestinal metaplasia (n = 118, 50.8%); GC (n = 684. 22.4%, P < 0.001)) was associated with poor prognosis (P < 0.001), advanced TNM stage (P = 0.05), and down-regulation of I kappa B-alpha expression (P < 0.001). Furthermore, MT2A was the independent prognostic signature segregated from the status of I kappa B-alpha and pathological features. In addition, MT2A inhibited cell growth through apoptosis and G2/M arrest, which negatively regulated NF-kappaB pathway through up-regulation of I kappa B-alpha and down-regulation of p-I kappa B-alpha and cyclin D1 expression. CONCLUSIONS: MT2A might play a tumor suppressive activity through inhibiting NF-kappaB signaling and may be a prognostic biomarker and potential target for individual therapy of GC patients.

[704]

TÍTULO / TITLE: - FIM-A, a phosphorus-containing sirolimus, inhibits the angiogenesis and proliferation of osteosarcomas.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Res. 2013;20(7):319-26.

AUTORES / AUTHORS: - Liu WN; Lin JH; Cheng YR; Zhang L; Huang J; Wu ZY; Wang FS; Xu SG; Lin WP; Lan WB; Yang GX

INSTITUCIÓN / INSTITUTION: - The First Clinical Medical College of Fujian Medical University, Fuzhou, Fujian, China.

RESUMEN / SUMMARY: - The mTOR pathway is a central control of cell growth, proliferation, metabolism, and survival, and is deregulated in most cancers. Cancer cells are addicted to increased activity of mTOR kinase-mediated signaling pathways, leading to numerous inhibitors of mTOR signaling in preclinic and clinical trials for cancer therapy. Phosphorus-containing sirolimus (FIM-A), which targets mTOR signaling, inhibits cancer cell growth in vitro. Here we report that FIM-A reduces the angiogenesis and proliferation of osteosarcoma both in vitro and in vivo. In cultured osteosarcoma cell lines, FIM-A inhibited cell proliferation and arrested cells in the G1 phase of the cell cycle, accompanied with reduction of VEGF and HIF-1alpha. With in vivo mouse osteosarcoma xenografts, FIM-A treatment resulted in the inhibition of mTORC1 signaling as demonstrated by the decreased phosphorylation of p70S6K1 and 4E-BP1. Consistent with this finding, FIM-A significantly decreased the average tumor volume, nuclei staining of PCNA, and the number of intratumoral microvessels. Our data demonstrated that targeting mTORC1 by FIM-A inhibited the growth of osteosarcoma in vitro and in vivo, providing the basis for further development of FIM-A as a therapy for osteosarcoma patients.

[705]

TÍTULO / TITLE: - Patients with recurrent biliary tract cancer have a better prognosis than those with unresectable disease: retrospective analysis of a multi-institutional experience with patients of advanced biliary tract cancer who received palliative chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Hepatobiliary Pancreat Sci. 2013 Jun 20. doi: 10.1002/jhbp.2.

●● Enlace al texto completo (gratis o de pago) [1002/jhbp.2](#)

AUTORES / AUTHORS: - Ikezawa K; Kanai M; Ajiki T; Tsukamoto T; Toyokawa H; Terajima H; Furuyama H; Nagano H; Ikai I; Kuroda N; Awane M; Ochiai T; Takemura S; Miyamoto A; Kume M; Ogawa M; Takeda Y; Taira K; Ioka T

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka, Osaka, 537-8511, Japan.
ikezawakenji@gh.med.osaka-u.ac.jp.

RESUMEN / SUMMARY: - BACKGROUND: Prognostic factors for patients with advanced biliary tract cancer (BTC) who received palliative chemotherapy have not been fully established. Especially, the status of unresectable/recurrent disease has not been well studied because of a small number of patients with recurrent BTC in previous studies. METHODS: This multicenter retrospective study was conducted in 18 institutions in Japan. We retrospectively reviewed data regarding 403 patients with pathologically proven BTC who received

palliative chemotherapy between April 2006 and March 2009. One hundred and ninety-two patients with recurrent BTC were included. Univariate and multivariate analyses were performed to identify prognostic factors. RESULTS: The median overall survival was significantly longer in the recurrent BTC patients than in the unresectable BTC patients (398 days vs. 323 days, $P = 0.004$). After adjustment using multivariate analysis, the status of recurrent/unresectable disease remained an independent prognostic factor (hazard ratio 1.33, 95% confidence interval 1.04-1.70, $P = 0.022$) in addition to performance status, extent of disease, carbohydrate antigen 19-9 levels, and carcinoembryonic antigen levels. CONCLUSIONS: The status of unresectable/recurrent disease was shown as an independent prognostic factor in the BTC patients. This result may help to predict life expectancy of BTC patients and design future clinical trials evaluating palliative chemotherapy in BTC.

[706]

TÍTULO / TITLE: - Estrogen-mediated mechanisms to control the growth and apoptosis of breast cancer cells: a translational research success story.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Vitam Horm. 2013;93:1-49. doi: 10.1016/B978-0-12-416673-8.00007-1.

●● Enlace al texto completo (gratis o de pago) [1016/B978-0-12-416673-8.00007-1](#)

AUTORES / AUTHORS: - McDaniel RE; Maximov PY; Jordan VC

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Georgetown University, Lombardi Comprehensive Cancer Center, Washington, District of Columbia, USA.

RESUMEN / SUMMARY: - The treatment and prevention of solid tumors have proved to be a major challenge for medical science. The paradigms for success in the treatment of childhood leukemia, Hodgkin's disease, Burkett's lymphoma, and testicular carcinoma with cytotoxic chemotherapy did not translate to success in solid tumors-the majority of cancers that kill. In contrast, significant success has accrued for patients with breast cancer with antihormone treatments (tamoxifen or aromatase inhibitors) that are proved to enhance survivorship, and remarkably, there are now two approved prevention strategies using either tamoxifen or raloxifene. This was considered impossible 40 years ago. We describe the major clinical advances with nonsteroidal antiestrogens that evolved into selective estrogen receptor modulators (SERMs) which successfully exploited the ER target selectively inside a woman's body. The standard paradigm that estrogen stimulates breast cancer growth has been successfully exploited for over 4 decades with therapeutic strategies that block (tamoxifen, raloxifene) or reduce (aromatase inhibitors) circulating estrogens in patients to stop breast tumor growth. But this did not explain why high-dose estrogen treatment that was the standard of care to treat postmenopausal

breast cancer for 3 decades before tamoxifen caused tumor regression. This paradox was resolved with the discovery that breast cancer resistance to long-term estrogen deprivation causes tumor regression with physiologic estrogen through apoptosis. The new biology of estrogen action has been utilized to explain the findings in the Women's Health Initiative that conjugated equine estrogen alone given to postmenopausal women, average age 68, will produce a reduction of breast cancer incidence and mortality compared to no treatment. Estrogen is killing nascent breast cancer cells in the ducts of healthy postmenopausal women. The modulation of the ER using multifunctional medicines called SERMs has provided not only significant improvements in women's health and survivorship not anticipated 40 years ago but also has been the catalyst to enhance our knowledge of estrogen's apoptotic action that can be further exploited in the future.

[707]

TÍTULO / TITLE: - Inactivation of HDAC3 and STAT3 is Critically Involved in 1-Stearoyl-sn-Glycero-3-Phosphocholine-Induced Apoptosis in Chronic Myelogenous Leukemia K562 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Jun 2.

- Enlace al texto completo (gratis o de pago) [1007/s12013-013-9670-0](http://dx.doi.org/10.1007/s12013-013-9670-0)

AUTORES / AUTHORS: - Jung JH; Jeong SJ; Kim JH; Jung SK; Jung DB; Lee D; Sohn EJ; Yun M; Lee HJ; Lee HJ; Kim SH

INSTITUCIÓN / INSTITUTION: - Cancer Preventive Material Development Research Center, College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 131-701, South Korea.

RESUMEN / SUMMARY: - We here investigated the anticancer mechanism of 1-stearoyl-sn-glycero-3-phosphocholine (LPC), one of the lysophosphatidylcholines, in chronic myelogenous leukemia (CML) K562 cells. LPC significantly showed cytotoxicity at 80 μM and induced apoptosis by sub-G1 accumulation, increase in Annexin V positive and caspase activation. LPC enhanced histone H3 acetylation but decreased histone deacetylase (HDAC) activity and HDAC3 expression. LPC also inhibited phosphorylation of STAT3, its DNA binding activity and nuclear co-localization of HDAC3 and STAT3. In addition, LPC effectively attenuated the expression of survival genes such as Cyclin D1, Cyclin E, Bcl-xL, Bcl-2 and survivin but did not affect COX-2 expression in K562 cells. Furthermore, LPC suppressed phosphorylation of Src and Janus activated kinase 2 while promoted the expression of tyrosine phosphatase Src homology 2 domain-containing phosphatase 1 (SHP-1). Consistently, silencing SHP-1 and pervanadate, an inhibitor of protein tyrosine phosphatase, reversed inactivation of HDAC and STAT3, cleavages of caspase 3 and poly (ADP-ribose) polymerase in LPC-induced apoptosis. Of

note, chromatin immunoprecipitation assay revealed that LPC suppressed the binding of HDAC3 and STAT3 to Bcl-xL, Bcl-2 and survivin promoter. Overall, our findings indicate that inactivation of STAT3 and HDAC mediates LPC-induced apoptosis in CML K562 cells.

[708]

TÍTULO / TITLE: - Therapeutic potential of the poly(ADP-ribose) polymerase inhibitor rucaparib for the treatment of sporadic human ovarian cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jun;12(6):1002-15. doi: 10.1158/1535-7163.MCT-12-0813. Epub 2013 May 31.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-0813](#)

AUTORES / AUTHORS: - Ihnen M; zu Eulenburg C; Kolarova T; Qi JW; Manivong K; Chalukya M; Dering J; Anderson L; Ginther C; Meuter A; Winterhoff B; Jones S; Velculescu VE; Venkatesan N; Rong HM; Dandekar S; Udar N; Janicke F; Los G; Slamon DJ; Konecny GE

INSTITUCIÓN / INSTITUTION: - Division of Hematology-Oncology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.

RESUMEN / SUMMARY: - Here, we investigate the potential role of the PARP inhibitor rucaparib (CO-338, formerly known as AG014699 and PF-01367338) for the treatment of sporadic ovarian cancer. We studied the growth inhibitory effects of rucaparib in a panel of 39 ovarian cancer cell lines that were each characterized for mutation and methylation status of BRCA1/2, baseline gene expression signatures, copy number variations of selected genes, PTEN status, and sensitivity to platinum-based chemotherapy. To study interactions with chemotherapy, we used multiple drug effect analyses and assessed apoptosis, DNA fragmentation, and gammaH2AX formation. Concentration-dependent antiproliferative effects of rucaparib were seen in 26 of 39 (67%) cell lines and were not restricted to cell lines with BRCA1/2 mutations. Low expression of other genes involved in homologous repair (e.g., BCCIP, BRCC3, ATM, RAD51L1), amplification of AURKA or EMSY, and response to platinum-based chemotherapy was associated with sensitivity to rucaparib. Drug interactions with rucaparib were synergistic for topotecan, synergistic, or additive for carboplatin, doxorubicin or paclitaxel, and additive for gemcitabine. Synergy was most pronounced when rucaparib was combined with topotecan, which resulted in enhanced apoptosis, DNA fragmentation, and gammaH2AX formation. Importantly, rucaparib potentiated chemotherapy independent of its activity as a single agent. PARP inhibition may be a useful therapeutic strategy for a wider range of ovarian cancers bearing deficiencies in the homologous recombination pathway other than just BRCA1/2 mutations. These results

support further clinical evaluation of rucaparib either as a single agent or as an adjunct to chemotherapy for the treatment of sporadic ovarian cancer.

[709]

TÍTULO / TITLE: - Galactose-Decorated Reduction-Sensitive Degradable Chimaeric Polymersomes as a Multifunctional Nanocarrier To Efficiently Chaperone Apoptotic Proteins into Hepatoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomacromolecules. 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1021/bm4007248](#)

AUTORES / AUTHORS: - Wang X; Sun H; Meng F; Cheng R; Deng C; Zhong Z

INSTITUCIÓN / INSTITUTION: - Biomedical Polymers Laboratory, and Jiangsu Key Laboratory of Advanced Functional Polymer Design and Application, Department of Polymer Science and Engineering, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China.

RESUMEN / SUMMARY: - Hepatoma-targeting reduction-sensitive chimaeric biodegradable polymersomes were designed and developed based on galactose-poly(ethylene glycol)-poly(epsilon-caprolactone) (Gal-PEG-PCL), PEG-PCL-poly(2-(diethylamino)ethyl methacrylate) (PEG-PCL-PDEA, asymmetric), and PEG-SS-PCL for facile loading and triggered intracellular delivery of proteins. The chimaeric polymersomes formed from PEG-PCL-PDEA and PEG-SS-PCL had a monodisperse distribution with average sizes ranging from 95.5 to 199.2 nm depending on PEG-SS-PCL contents. Notably, these polymersomes displayed decent loading of bovine serum albumin (BSA), ovalbumin (OVA), and cytochrome C (CC) proteins likely due to presence of electrostatic and hydrogen bonding interactions between proteins and PDEA block located in the interior of polymersomes. The in vitro release studies showed that protein release was largely accelerated under a reductive condition containing 10 mM dithiothreitol (DTT). For example, ca. 77.2 and 22.1% of FITC-BSA were released from CP(SS50) (chimaeric polymersomes containing 50 wt % PEG-SS-PCL) at 37 degrees C in 12 h in the presence and absence of 10 mM DTT, respectively. Confocal microscopy showed that FITC-CC-loaded Gal-decorated CP(SS40) could efficiently deliver and release FITC-CC into HepG2 cells following 24 h treatment, in contrast to little or negligible fluorescence detected in HepG2 cells treated with FITC-CC-loaded nontargeting polymersomes or free CC. MTT assays revealed that CC-loaded Gal-decorated CP(SS40) exhibited apparent targetability and pronounced antitumor activity to HepG2 cells, in which cell viabilities decreased from 81.9, 60.6, 49.5, 42.2 to 31.5% with increasing Gal-PEG-PCL contents from 0, 10, 20, 30 to 40 wt %. Most remarkably, granzyme B-loaded Gal-decorated chimaeric polymersomes effectively caused apoptosis of HepG2 cells with a markedly low half-maximal inhibitory concentration (IC50) of 2.7 nM. These reduction-

responsive chimaeric biodegradable polymersomes offer a multifunctional platform for efficient intracellular protein delivery.

[710]

TÍTULO / TITLE: - Epigenetic silencing of the WNT antagonist Dickkopf 3 disrupts normal Wnt/beta-catenin signalling and apoptosis regulation in breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cell Mol Med. 2013 Jul 24. doi: 10.1111/jcmm.12099.

●● Enlace al texto completo (gratis o de pago) [1111/jcmm.12099](#)

AUTORES / AUTHORS: - Xiang T; Li L; Yin X; Zhong L; Peng W; Qiu Z; Ren G; Tao Q

INSTITUCIÓN / INSTITUTION: - Molecular Oncology and Epigenetics Laboratory, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

RESUMEN / SUMMARY: - Dickkopf-related protein 3 (DKK3) is an antagonist of Wnt ligand activity. Reduced DKK3 expression has been reported in various types of cancers, but its functions and related molecular mechanisms in breast tumorigenesis remain unclear. We examined the expression and promoter methylation of DKK3 in 10 breast cancer cell lines, 96 primary breast tumours, 43 paired surgical margin tissues and 16 normal breast tissues. DKK3 was frequently silenced in breast cell lines (5/10) by promoter methylation, compared with human normal mammary epithelial cells and tissues. DKK3 methylation was detected in 78% of breast tumour samples, whereas only rarely methylated in normal breast and surgical margin tissues, suggesting tumour-specific methylation of DKK3 in breast cancer. Ectopic expression of DKK3 suppressed cell colony formation through inducing G0/G1 cell cycle arrest and apoptosis of breast tumour cells. DKK3 also induced changes of cell morphology, and inhibited breast tumour cell migration through reversing epithelial-mesenchymal transition (EMT) and down-regulating stem cell markers. DKK3 inhibited canonical Wnt/beta-catenin signalling through mediating beta-catenin translocation from nucleus to cytoplasm and membrane, along with reduced active-beta-catenin, further activating non-canonical JNK signalling. Thus, our findings demonstrate that DKK3 could function as a tumour suppressor through inducing apoptosis and regulating Wnt signalling during breast tumorigenesis.

[711]

TÍTULO / TITLE: - Revisiting Clinical Trials Using EGFR Inhibitor-Based Regimens in Patients with Advanced Non-Small Cell Lung Cancer: A Retrospective Analysis of an MD Anderson Cancer Center Phase I Population.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncotarget. 2013 May;4(5):772-84.

AUTORES / AUTHORS: - Wheler J; Falchook G; Tsimberidou AM; Hong D; Naing A; Piha-Paul S; Chen SS; Heymach J; Fu S; Stephen B; Fok JY; Janku F; Kurzrock R

INSTITUCIÓN / INSTITUTION: - Department of Investigational Cancer Therapeutics - a Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Texas.

RESUMEN / SUMMARY: - Purpose: Single-agent EGFR inhibitor therapy is effective mainly in patients with lung cancer and EGFR mutations. Treating patients who develop resistance, or who are insensitive from the outset, often because of resistant mutations, other aberrations or the lack of an EGFR mutation, probably requires rational combinations. We therefore investigated the outcome of EGFR inhibitor-based combination regimens in patients with heavily-pretreated non-small cell lung cancer (NSCLC) referred to a Phase I Clinic. Methods: We reviewed the electronic records of patients with NSCLC treated with an EGFR inhibitor-based combination regimen: erlotinib and cetuximab; erlotinib, cetuximab and bevacizumab; erlotinib and dasatinib; erlotinib and bortezomib; or cetuximab and sirolimus. Results: EGFR mutations were detected in 16% of patients (21/131). EGFR inhibitor-based combination regimens were administered to 15 patients with EGFR-mutant NSCLC and 24 with EGFR wild-type disease. Stable disease (SD) \geq 6 months/partial remission (PR) was attained in 20% of EGFR-mutant patients (3/15; two with sensitive mutations and secondary resistance to prior erlotinib, and one with a resistant mutation), as well as 26% of evaluable patients (5/19) with wild-type disease. One of three evaluable patients with squamous cell histology achieved SD for 26.5 months (EGFR wild-type, TP53-mutant, regimen=erlotinib, cetuximab and bevacizumab). Conclusions: Eight of 34 evaluable patients (24%) with advanced, refractory NSCLC evaluable for response achieved SD \geq 6 months/PR (PR=3; SD \geq 6 months=5) on EGFR inhibitor-based combination regimens (erlotinib, cetuximab; erlotinib, cetuximab and bevacizumab; and, erlotinib, bortezomib), including patients with secondary resistance to single-agent EGFR inhibitors, resistant mutations, wild-type disease, and, squamous histology.

[712]

TÍTULO / TITLE: - IKZF1 and CRLF2 gene alterations correlate with poor prognosis in Japanese BCR-ABL1-negative high-risk B-cell precursor acute lymphoblastic leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Pediatr Blood Cancer*. 2013 Oct;60(10):1587-92. doi: 10.1002/pbc.24571. Epub 2013 Jun 27.

●● [Enlace al texto completo \(gratis o de pago\) 1002/pbc.24571](#)

AUTORES / AUTHORS: - Yamashita Y; Shimada A; Yamada T; Yamaji K; Hori T; Tsurusawa M; Watanabe A; Kikuta A; Asami K; Saito AM; Horibe K

INSTITUCIÓN / INSTITUTION: - National Hospital Organization Nagoya Medical Center Clinical Research Center, Nagoya, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Genome-wide analysis studies have demonstrated that IKZF1, CRLF2, and JAK2 gene alterations correlate with poor prognosis in pediatric B-cell precursor acute lymphoblastic leukemia (BCP-ALL). However, the prognostic significance for these gene alterations has not been clarified in Japanese patients. PROCEDURE: A total of 194 patients with BCP-ALL enrolled in the Japanese Children's Cancer & Leukemia Study Group ALL 2004 clinical trial were assessed for the presence of three different gene alterations: IKZF1 deletions, CRLF2 expression and JAK2 mutation. RESULTS: IKZF1 deletions and CRLF2-high expression were identified in 22 of 177 (12%) patients and in 15 of 141 (11%) patients, respectively. However, JAK2 R683 mutation was detected only one of 177 patients. The 4-year event-free survival (4y-EFS) was different when comparing patients with or without IKZF1 deletions (68.2% vs. 85.2%; P = 0.04) and was also different when comparing patients with different CRLF2 expression levels (high, 66.7% vs. low, 88.1%; P = 0.03). The differences in 4y-EFS were statistically significant in patients with ALL in the National Cancer Institute (NCI)-high risk group (HR-ALL) (IKZF1 deletions: yes, 58.3% vs. no, 87.0%, P = 0.02; CRLF2 expression: high, 55.6% vs. low, 85.3%, P = 0.04) but not in patients with ALL in the NCI-standard risk group (SR-ALL; IKZF1 deletions: yes, 80.0% vs. no, 84.4%, P = 0.75; CRLF2 expression: high, 83.3% vs. low, 89.2%, P = 0.77). Coexistence of IKZF1 deletions and CRLF2-high expression associated with poor outcomes. CONCLUSIONS: IKZF1 deletions and CRLF2-high expression predicted poor outcomes in patients with HR-ALL but not in patients with SR-ALL in our Japanese cohort. *Pediatr Blood Cancer* 2013;60:1587-1592. © 2013 Wiley Periodicals, Inc.

[713]

TÍTULO / TITLE: - Temozolomide downregulates P-glycoprotein expression in glioblastoma stem cells by interfering with the Wnt3a/glycogen synthase-3 kinase/beta-catenin pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - *Neuro Oncol.* 2013 Jul 28.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not104](#)

AUTORES / AUTHORS: - Riganti C; Salaroglio IC; Caldera V; Campia I; Kopecka J; Mellai M; Annovazzi L; Bosia A; Ghigo D; Schiffer D

INSTITUCIÓN / INSTITUTION: - Department of Oncology, University of Turin, Turin, Italy (C.R., I.C.S., I.C., J.K., A.B., D.G.); Center for Experimental Research and Medical Studies, University of Turin, Turin, Italy (C.R., A.B., D.G.); Neuro-bio-oncology Center, Policlinico di Monza Foundation, Vercelli, Italy (V.C., M.M., L.A., D.S.).

RESUMEN / SUMMARY: - Background Glioblastoma multiforme stem cells display a highly chemoresistant phenotype, whose molecular basis is poorly known. We aim to clarify this issue and to investigate the effects of temozolomide on chemoresistant stem cells. Methods A panel of human glioblastoma cultures, grown as stem cells (neurospheres) and adherent cells, was used. Results Neurospheres had a multidrug resistant phenotype compared with adherent cells. Such chemoresistance was overcome by apparently noncytotoxic doses of temozolomide, which chemosensitized glioblastoma cells to doxorubicin, vinblastine, and etoposide. This effect was selective for P-glycoprotein (Pgp) substrates and for stem cells, leading to an investigation of whether there was a correlation between the expression of Pgp and the activity of typical stemness pathways. We found that Wnt3a and ABCB1, which encodes for Pgp, were both highly expressed in glioblastoma stem cells and reduced by temozolomide. Temozolomide-treated cells had increased methylation of the cytosine-phosphate-guanine islands in the Wnt3a gene promoter, decreased expression of Wnt3a, disrupted glycogen synthase-3 kinase/beta-catenin axis, reduced transcriptional activation of ABCB1, and a lower amount and activity of Pgp. Wnt3a overexpression was sufficient to transform adherent cells into neurospheres and to simultaneously increase proliferation and ABCB1 expression. On the contrary, glioblastoma stem cells silenced for Wnt3a lost the ability to form neurospheres and reduced at the same time the proliferation rate and ABCB1 levels. Conclusions Our work suggests that Wnt3a is an autocrine mediator of stemness, proliferation, and chemoresistance in human glioblastoma and that temozolomide may chemosensitize the stem cell population by downregulating Wnt3a signaling.

[714]

TÍTULO / TITLE: - Early post-bevacizumab progression on contrast-enhanced MRI as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 Central Reader Study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neuro Oncol. 2013 Jul;15(7):945-54. doi: 10.1093/neuonc/not049. Epub 2013 Jun 19.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not049](#)

AUTORES / AUTHORS: - Boxerman JL; Zhang Z; Safriel Y; Larvie M; Snyder BS; Jain R; Chi TL; Sorensen AG; Gilbert MR; Barboriak DP

INSTITUCIÓN / INSTITUTION: - Corresponding Author: Jerrold L. Boxerman, MD, PhD, Rhode Island Hospital, Department of Diagnostic Imaging, 593 Eddy St., Providence, RI 02903. jboxerman@lifespan.org.

RESUMEN / SUMMARY: - Background RTOG 0625/ACRIN 6677 is a multicenter, randomized, phase II trial of bevacizumab with irinotecan or temozolomide in recurrent glioblastoma (GBM). This study investigated whether early posttreatment progression on FLAIR or postcontrast MRI assessed by central

reading predicts overall survival (OS). Methods Of 123 enrolled patients, 107 had baseline and at least 1 posttreatment MRI. Two central neuroradiologists serially measured bidimensional (2D) and volumetric (3D) enhancement on postcontrast T1-weighted images and volume of FLAIR hyperintensity. Progression status on all posttreatment MRIs was determined using Macdonald and RANO imaging threshold criteria, with a third neuroradiologist adjudicating discrepancies of both progression occurrence and timing. For each MRI pulse sequence, Kaplan-Meier survival estimates and log-rank test were used to compare OS between cases with or without radiologic progression. Results Radiologic progression occurred after 2 chemotherapy cycles (8 weeks) in 9 of 97 (9%), 9 of 73 (12%), and 11 of 98 (11%) 2D-T1, 3D-T1, and FLAIR cases, respectively, and 34 of 80 (43%), 21 of 58 (36%), and 37 of 79 (47%) corresponding cases after 4 cycles (16 weeks). Median OS among patients progressing at 8 or 16 weeks was significantly less than that among nonprogressors, as determined on 2D-T1 (114 vs 278 days and 214 vs 426 days, respectively; $P < .0001$ for both) and 3D-T1 (117 vs 306 days [$P < .0001$] and 223 vs 448 days [$P = .0003$], respectively) but not on FLAIR (201 vs 276 days [$P = .38$] and 303 vs 321 days [$P = .13$], respectively). Conclusion Early progression on 2D-T1 and 3D-T1, but not FLAIR MRI, after 8 and 16 weeks of anti-vascular endothelial growth factor therapy has highly significant prognostic value for OS in recurrent GBM.

[715]

TÍTULO / TITLE: - The in vitro apoptotic effects of A248 and A1659, newly synthetic histone deacetylase inhibitors in oral cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oral Dis. 2013 Jul 1. doi: 10.1111/odi.12161.

●● Enlace al texto completo (gratis o de pago) [1111/odi.12161](#)

AUTORES / AUTHORS: - Shin JA; Han G; Park SK; Lee K; Kim HJ; Cho SD; Kim H

INSTITUCIÓN / INSTITUTION: - Department of Oral Pathology, School of Dentistry, Institute of Oral Bioscience, Chonbuk National University, Jeonju, Korea.

RESUMEN / SUMMARY: - OBJECTIVES: Histone deacetylase (HDAC) inhibitors represent potential therapeutic agents against various cancers. In this study, we attempt to identify whether newly synthesized HDAC inhibitors, A248 and A1659, can be effective anti-cancer drug candidates for oral cancer.

MATERIALS AND METHODS: The anti-cancer activities of A248 and A1659 in MC-3 and HN22 human oral cancer cells were evaluated by 3-(4,5-dimethylthiazol-20yl)-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium (MTS) assay, 4'-6-diamidino-2-phenylindole (DAPI) staining, Western blot analysis, immunocytochemistry, and small interference RNA (siRNA) technology. **RESULTS:** A248 and A1659 enhanced histone acetylation and decreased the viability of MC-3 and HN22 cells. A248 and A1659 also induced

apoptosis, as evidenced by altered nuclear features and poly(ADP-ribose)polymerase (PARP) cleavage. A248 and A1659 markedly decreased Sp1 expression in a concentration- or time-dependent manner and blocked nuclear translocation of Sp1 protein from the cytosol, which contributed to an increase in p27 expression and a decrease in cyclin D1 expression. Furthermore, the knockdown of Sp1 protein with siRNA caused marked alteration of p27 and cyclin D1 expression to induce apoptosis. The most popular HDAC inhibitor, trichostatin A (TSA) also induced apoptosis and reduced the expression level of Sp1 protein. CONCLUSION: These results suggest that A248 and A1659, two new HDAC inhibitors, may be attractive therapeutic drug candidates for targeting Sp1 in human oral cancer cells.

[716]

TÍTULO / TITLE: - Apoptosis of Human Pancreatic Carcinoma PC-2 Cells by an Antisense Oligonucleotide Specific to Point Mutated K-ras.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pathol Oncol Res. 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1007/s12253-013-9661-](#)

[X](#)

AUTORES / AUTHORS: - Yongxiang W; Liang G; Qinshu S

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Zhejiang Provincial People's Hospital, Hangzhou, 310014, China.

RESUMEN / SUMMARY: - The prognosis of pancreatic carcinoma is poor due to the difficulty in early diagnosis, insensitivity to routine therapies and limited understanding of its pathological mechanisms. Gene therapy is now becoming an important strategy for the treatment of pancreatic carcinoma, which includes antisense gene therapy. In this study, we investigated the effect of an antisense oligonucleotide specific to point mutated K-ras on the apoptosis of human pancreatic carcinoma cells in vitro. Human pancreatic carcinoma PC-2 cells were transfected with an antisense oligonucleotide specific to a K-ras point mutation by liposomes. The effect of the antisense oligonucleotide on the apoptosis of PC-2 cells was studied using flow cytometry, TUNEL, and phase contrast microscopy. An apoptotic peak was observed in the experimental group, and most cells were arrested at the G1 phase with few cells at the S phase. The numbers of apoptotic cells in the experimental group increased as indicated by TUNEL and phase contrast microscopy. An antisense oligonucleotide specific to a K-ras point mutation promotes apoptosis in PC-2 cells in vitro perhaps by inhibition of ras gene expression.

[717]

TÍTULO / TITLE: - Propofol inhibits invasion and enhances paclitaxel- induced apoptosis in ovarian cancer cells through the suppression of the transcription factor slug.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur Rev Med Pharmacol Sci. 2013 Jul;17(13):1722-9.

AUTORES / AUTHORS: - Wang P; Chen J; Mu LH; Du QH; Niu XH; -Y Zhang M

INSTITUCIÓN / INSTITUTION: - Department of Anesthesiology, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, Shandong Province, China. slyyzmy@126.com.

RESUMEN / SUMMARY: - BACKGROUND AND AIM: Propofol is one of the most commonly used intravenous anaesthetic agents during cancer resection surgery. It has recently found that propofol has the effect to inhibit cancer cell migration and invasion and sensitize cancer cells to chemotherapy. However, the role of the propofol on the ovarian cancer cells is unknown. In the present study, we explored the effect of propofol on invasion and chemosensitization of ovarian cancer cells to paclitaxel. MATERIALS AND METHODS: The paclitaxel sensitivity of ovarian cancer cell lines HO-8910PM, H0-8910, SKOV-3, OVCAR-3, COC1 and ES-2 were determined by MTT assays. The Slug levels in the cell lines and the effects of propofol on Slug levels in the cell lines were determined by western blot assays. The effect of propofol on invasion, migration and paclitaxel-induced ovarian cancer apoptosis was determined by Boyden chamber assays, cell MTT, TUNEL assays. RESULTS: The results showed that the cell lines COC1, H0-8910 and ES-2 were sensitive, whereas HO-8910PM, OVCAR-3, SKOV-3, were resistant to paclitaxel. Significant correlation was observed between basal Slug levels and paclitaxel sensitivity. Paclitaxel treatment increased Slug levels. Treatment with propofol induced apoptosis and increased paclitaxel killing of all paclitaxel-sensitive and -resistant ovarian cancer cells followed by significant decrease in the Slug levels. Treatment with propofol inhibits invasion and migration. CONCLUSIONS: These data suggest a new mechanism by which the propofol inhibits invasion and metastasis, enhances paclitaxel-induced ovarian cancer cell apoptosis through suppression of Slug.

[718]

TÍTULO / TITLE: - The clinical significance of apoptosis and M30 expression in colonic cancer progression.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Recept Signal Transduct Res. 2013 Aug;33(4):255-9. doi: 10.3109/10799893.2013.802804. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago)

[3109/10799893.2013.802804](https://doi.org/10.3109/10799893.2013.802804)

AUTORES / AUTHORS: - Kykalos S; Dimitroulis D; Ntikoudi E; Karayiannakis A

INSTITUCIÓN / INSTITUTION: - 2nd Department of Surgery, Democritus University of Thrace , Alexandroupolis and.

RESUMEN / SUMMARY: - Abstract Background/aim: The aim of this study is to identify the significance of M30, an early apoptosis indicator, in colorectal cancer and its liver metastasis. Patients and methods: The expression of M30 was immunohistochemically estimated at colonic and liver metastatic tissues of 66 patients. The results were correlated to clinical and pathological features of the tumors. Results: High expression of M30 was observed in 15.5% of cases. No metastatic tissue showed expression of M30, while stage D tumors (metastasis included) showed a statistic significant lower expression of M30, when compared to earlier tumor stages. Conclusion: Low expression of M30 implies the development of resistance mechanisms against apoptosis, facilitating the progression of colon cancer.

[719]

TÍTULO / TITLE: - Perilla oil and exercise decrease expressions of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 and highly sensitive C-reactive protein in patients with hyperlipidemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Tradit Chin Med. 2013 Apr;33(2):170-5.

AUTORES / AUTHORS: - Wei M; Xiong P; Zhang L; Fei M; Chen A; Li F

INSTITUCIÓN / INSTITUTION: - First Affiliated Hospital to Soochow University, Suzhou 215006, China. weimg@sina.com

RESUMEN / SUMMARY: - OBJECTIVE: To verify the effects of perilla oil on the regulation of blood lipid levels in patients with hyperlipidemia. METHODS: Blood was taken from patients prior to and 8 weeks following treatment with perilla oil. Different ways to test for indexes which correlate to hyperlipidemia were performed. Some indexes, which correlate with inflammation and injury to endothelial cells, were tested using enzyme linked immunosorbent assays. RESULTS: Serum lipid levels [triglyceride (TG), total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C)] changed significantly after 56 days of treatment. Differences were noted as early as 28 days after treatment began (P < 0.05). Treatment with perilla oil showed statistically significant recovery levels of high-density lipoprotein-cholesterol (HDL-C) after 28 and 56 days of treatment. Plasma lipids levels were significantly lower after 56 days of treatment (P < 0.05). Perilla oil reduced blood lipid levels in patients, and the regulation of cell signaling factor levels had no adverse effects on patients' liver or kidney function, or blood routine examinations. CONCLUSION: Perilla oil treatment is safe in clinical use, can regulate blood lipid levels and protects the function of endothelial cells.

[720]

TÍTULO / TITLE: - Inhibition of oncogenic Pim-3 kinase modulates transformed growth and chemosensitizes pancreatic cancer cells to gemcitabine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun;14(6):492-501. doi: 10.4161/cbt.24343.

●● Enlace al texto completo (gratis o de pago) [4161/cbt.24343](#)

AUTORES / AUTHORS: - Xu D; Cobb MG; Gavilano L; Witherspoon SM; Williams D; White CD; Taverna P; Bednarski BK; Kim HJ; Baldwin AS; Baines AT

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Marine Environmental Science, Xiamen University, Xiamen, China.

RESUMEN / SUMMARY: - Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with a 5-year survival rate of only 6%. Although the cytosine analog gemcitabine is the drug commonly used to treat PDAC, chemoresistance unfortunately renders the drug ineffective. Thus, strategies that can decrease this resistance will be essential for improving the dismal outcome of patients suffering from this disease. We previously observed that oncogenic Pim-1 kinase was aberrantly expressed in PDAC tissues and cell lines and was responsible for radioresistance. Furthermore, members of the Pim family have been shown to reduce the efficacy of chemotherapeutic drugs in cancer. Therefore, we attempted to evaluate the role of Pim-3 in chemoresistance of PDAC cells. We were able to confirm upregulation of the Pim-3 oncogene in PDAC tissues and cell lines versus normal samples. Biological consequences of inhibiting Pim-3 expression with shRNA-mediated suppression included decreases in anchorage-dependent growth, invasion through Matrigel and chemoresistance to gemcitabine as measured by caspase-3 activity. Additionally, we were able to demonstrate that Pim-1 and Pim-3 play overlapping but non-identical roles as it relates to gemcitabine sensitivity of pancreatic cancer cells. To further support the role of Pim-3 suppression in sensitizing PDAC cells to gemcitabine, we used the pharmacological Pim kinase inhibitor SGI-1776. Treatment of PDAC cells with SGI-1776 resulted in decreased phosphorylation of the proapoptotic protein Bad and cell cycle changes. When SGI-1776 was combined with gemcitabine, there was a greater decrease in cell viability in the PDAC cells versus cells treated with either of the drugs separately. These results suggest combining drug therapies that inhibit Pim kinases, such as Pim-3, with chemotherapeutic agents, to aid in decreasing chemoresistance in pancreatic cancer.

[721]

TÍTULO / TITLE: - Inhibition of checkpoint kinase 2 (CHK2) enhances sensitivity of pancreatic adenocarcinoma cells to gemcitabine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cell Mol Med. 2013 Jul 16. doi: 10.1111/jcmm.12101.

●● Enlace al texto completo (gratis o de pago) [1111/jcmm.12101](#)

AUTORES / AUTHORS: - Duong HQ; Hong YB; Kim JS; Lee HS; Yi YW; Kim YJ; Wang A; Zhao W; Cho CH; Seong YS; Bae I

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; WCU (World Class University) Research Center of Nanobiomedical Science, Dankook University, Cheonan, Korea.

RESUMEN / SUMMARY: - Checkpoint kinase 2 (CHK2) plays pivotal function as an effector of cell cycle checkpoint arrest following DNA damage. Recently, we found that co-treatment of NSC109555 (a potent and selective CHK2 inhibitor) potentiated the cytotoxic effect of gemcitabine (GEM) in pancreatic cancer MIA PaCa-2 cells. Here, we further examined whether NSC109555 could enhance the antitumour effect of GEM in pancreatic adenocarcinoma cell lines. In this study, the combination treatment of NSC109555 plus GEM demonstrated strong synergistic antitumour effect in four pancreatic cancer cells (MIA PaCa-2, CFPAC-1, Panc-1 and BxPC-3). In addition, the GEM/NSC109555 combination significantly increased the level of intracellular reactive oxygen species (ROS), accompanied by induction of apoptotic cell death. Inhibition of ROS generation by N-acetyl cysteine (NAC) significantly reversed the effect of GEM/NSC109555 in apoptosis and cytotoxicity. Furthermore, genetic knockdown of CHK2 by siRNA enhanced GEM-induced apoptotic cell death. These findings suggest that inhibition of CHK2 would be a beneficial therapeutic approach for pancreatic cancer therapy in clinical treatment.

[722]

TÍTULO / TITLE: - Outcome After Failure of Second Generation Tyrosine Kinase Inhibitors Treatment As First-line Therapy for Patients With Chronic Myeloid Leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Aug;13(4):477-84. doi: 10.1016/j.clml.2013.02.025. Epub 2013 Jun 14.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.02.025

AUTORES / AUTHORS: - Eghtedar A; Kantarjian H; Jabbour E; O'Brien S; Burton E; Garcia-Manero G; Verstovsek S; Ravandi F; Borthakur G; Konopleva M; Quintas-Cardama A; Cortes J

INSTITUCIÓN / INSTITUTION: - Leukemia Department, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

RESUMEN / SUMMARY: - INTRODUCTION: The outcome of patients with CML who discontinue 2G-TKI initial therapy is unknown. We analyzed the characteristics of patients in whom treatment with first-line 2G-TKIs had failed. PATIENTS AND METHODS: A total of 218 patients with CML were treated with dasatinib (n = 101) or nilotinib (n = 117; 12 in AP). After a median follow-up of 23 months, 40 patients (18%) discontinued therapy: 25 initially treated with nilotinib (21% of all treated with nilotinib; 6 treated in AP) and 15 (15%) initially

treated with dasatinib. Median age of the patients was 47 (range, 19-79) years, and they had received therapy for a median of 8 (range, 0-62) months.

RESULTS: Reasons for treatment discontinuation include: toxicity, 16 patients; resistance in CP, 5 patients; transformation to blast phase, 4 patients (2 treated in AP); and other reasons, 15 patients. Subsequent treatment was imatinib in 11 patients, nilotinib in 7, dasatinib in 4, ponatinib in 2, chemotherapy plus dasatinib in 3, stem cell transplant in 2, bafetinib in 1, and unknown or none in 8 patients. A complete cytogenetic response was achieved in 19 patients, including 17 with major molecular response. Fourteen of the patients who achieved a complete molecular response or major molecular response with subsequent TKIs were in CP at the time of 2G-TKI discontinuation.

CONCLUSION: We conclude that treatment failure after first-line therapy with 2G-TKIs is mostly associated with toxicity or patient preference, and these patients respond well to alternative TKIs.

[723]

TÍTULO / TITLE: - Thyroid dysfunction and tyrosine kinase inhibitors in renal cell carcinoma treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Endocr Relat Cancer. 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1530/ERC-13-0201](#)

AUTORES / AUTHORS: - Bianchi L; Rossi L; Tomao F; Papa A; Zoratto F; Tomao S

INSTITUCIÓN / INSTITUTION: - L Bianchi, Department of Medico-Surgical Sciences and Biotechnologies, Oncology Unit - ICOT, "Sapienza" University of Rome, Latina, Italy.

RESUMEN / SUMMARY: - The incidence of kidney cancer has increased worldwide in the last years. Although the most common type of kidney cancer is localized RCC, with a 5-year survival rate of 85%, about one third of patients present advanced or metastatic disease at diagnosis, with a 5-year survival rate of only 10%. Multitargeted receptor tyrosine kinase inhibitors (sunitinib and sorafenib), the anti-VEGF monoclonal antibody bevacizumab in association with interferon-alfa, the mTOR inhibitors are now approved for the treatment of mRCC. Recently the novel agents pazopanib and axitinib have also demonstrated efficacy in mRCC patients. Several recent retrospective and prospective trials have suggested that some of their adverse events, such as hypertension, hypothyroidism and HFS, may act as potential biomarkers of response and efficacy of treatment. In this review we analyzed the studies which have suggested a relationship between hypothyroidism onset and a better outcome of mRCC patients treated with tyrosine kinase inhibitors. The biological mechanisms suggesting and explaining this correlation are not well known and different speculative theories have been considered in order to investigate the clinical link between hypothyroidism occurrence and the prolonged therapy with tyrosine kinase inhibitors in solid tumors. Furthermore,

the management of this unexplained side effect is very important to maximize the efficacy of therapy in mRCC patients, because there is a clear and consistent relationship between drug dose and efficacy of treatment. Certainly other studies are needed to clarify if a better outcome is associated to hypothyroidism induced to tyrosine kinase inhibitors in patients with mRCC.

[724]

TÍTULO / TITLE: - Health Care Disparities in the Treatment of Colorectal Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Curr Treat Options Oncol. 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [1007/s11864-013-0241-](#)

[9](#)

AUTORES / AUTHORS: - Dorsey K; Zhou Z; Masaoud R; Nimeiri HS

INSTITUCIÓN / INSTITUTION: - Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA.

RESUMEN / SUMMARY: - OPINION STATEMENT: Treatment of colorectal carcinoma remains challenging, especially in patients with recurrent or metastatic disease. Despite advances in screening and treatment of this cancer, health care disparities remain one of the major yet amendable factors that can lead to differences in outcomes. As clinicians, we need to be aware of such disparities to better tailor our screening and treatment interventions for our patients. Knowing that socioeconomic status, educational status, and personal beliefs contribute to racial disparities in this disease, as clinicians we should strive to know our patients and their beliefs to help minimize this discrepancy. Additionally, we need to maintain and advance our knowledge by keeping up with all clinical and translational research in the field and create strategies to increase enrollment of racial minorities in clinical trials. While conventional chemotherapies continue to play a vital role, it is becoming more and more evident that treatment strategies need to be personalized. Understanding the molecular biology of cancer has changed the landscape of new therapies. Future research needs to be directed towards understanding genetic, biological, and pharmacogenetic and genomic contributors to the development of disease and treatment responses.

[725]

TÍTULO / TITLE: - Tomatoes and stroke prevention. New evidence shows lycopene is not just a cancer fighter.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Harv Health Lett. 2013 Feb;38(4):4.

[726]

TÍTULO / TITLE: - BCL11A overexpression predicts survival and relapse in non-small cell lung cancer and is modulated by microRNA-30^a and gene amplification.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer. 2013 Jun 12;12:61. doi: 10.1186/1476-4598-12-61.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-61](#)

AUTORES / AUTHORS: - Jiang BY; Zhang XC; Su J; Meng W; Yang XN; Yang JJ; Zhou Q; Chen ZY; Chen ZH; Xie Z; Chen SL; Wu YL

INSTITUCIÓN / INSTITUTION: - Guangdong Lung Cancer Institute, 106 Zhongshan Er Rd, Guangzhou, 510080, China.

RESUMEN / SUMMARY: - BACKGROUND: Aberrant activation of the proto-oncogene B-cell lymphoma/leukemia 11^a (BCL11A) has been implicated in the pathogenesis of leukemia and lymphoma. However, the clinical significance of BCL11A in non-small cell lung cancer (NSCLC) remains unknown. RESULTS: We examined BCL11A expression at the protein and mRNA levels in a cohort (n=114) of NSCLC patients and assessed the relationship between BCL11A expression and clinicopathological parameters. Data from array-based Comparative Genomic Hybridization (aCGH) and microRNA transfection experiments were integrated to explore the potential mechanisms of abnormal BCL11A activation in NSCLC. Compared to adjacent non-cancerous lung tissues, BCL11A expression levels were specifically upregulated in NSCLC tissues at both the mRNA (t=9.81, P<0.001) and protein levels. BCL11A protein levels were higher in patients with squamous histology (chi²=15.81, P=0.001), smokers (chi²=8.92, P=0.004), patients with no lymph node involvement (chi²=5.14, P=0.029), and patients with early stage disease (chi²=3.91, P=0.048). A multivariate analysis demonstrated that in early stage NSCLC (IA-IIIB), BCL11A was not only an independent prognostic factor for disease-free survival (hazards ratio [HR] 0.24, 95% confidence interval [CI] 0.12-0.50, P<0.001), but also for overall survival (HR=0.23, 95% CI 0.09-0.61, P=0.003). The average BCL11A expression level was much higher in SCC samples with amplifications than in those without amplifications (t=3.30, P=0.023). Assessing functionality via an in vitro luciferase reporter system and western blotting, we found that the BCL11A protein was a target of miR-30^a. CONCLUSIONS: Our results demonstrated that proto-oncogene BCL11A activation induced by miR-30^a and gene amplification may be a potential diagnostic and prognostic biomarker for effective management of this disease.

[727]

TÍTULO / TITLE: - Ethacrynic acid oxadiazole analogues induce apoptosis in malignant hematological cells through down-regulation of Mcl-1 and c-FLIP which was attenuated by GSTP1-1.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1224](#)

AUTORES / AUTHORS: - Liu G; Wang R; Wang Y; Li P; Zhao G; Zhao L; Jing Y

INSTITUCIÓN / INSTITUTION: - 1Pharmacology, Shenyang Pharmaceutical University.

RESUMEN / SUMMARY: - Ethacrynic acid (EA), a diuretic, inhibits glutathione S-transferase P1-1 (GSTP1-1) activity and induces cell death in malignant cells at high concentrations. To improve EA activity, EA oxadiazole analogues 6s and 6u were synthesized. Although both compounds have greater antiproliferative effects than EA in human HL-60 cells, 6u has a reduced ability to inhibit GSTP1-1 activity. The mechanisms of both 6s- and 6u-induced cell death as well as the role of GSTP1-1 in their actions were studied. Both 6s and 6u equally induced apoptosis in HL-60 cells due to the activation of caspase-3,-9 and -8, which was correlated with the down-regulation of antiapoptotic proteins c-FLIP, Mcl-1, and XIAP. The caspase inhibitor Z-VAD-FMK blocked the reduction of XIAP, but not of c-FLIP and Mcl-1, in 6s-treated cells. The reduction of c-FLIP and Mcl-1 by 6s was not blocked by the proteasomal inhibitor MG132, but was correlated with inhibition of the phosphorylation of ERK and eIF4E. Both 6s and 6u decreased the intracellular glutathione (GSH) levels. N-acetylcysteine blocked reduction in the levels of Mcl-1, c-FLIP and intracellular GSH as well as apoptosis in HL-60 cells treated by either compound. Silencing of GSTP1-1 in K562 cells sensitized, but overexpression of GSTP1-1 in Raji cells blocked, apoptosis induction by either compound. GSH conjugation at the methylene group abrogated the ability of inducing apoptosis. These data suggest that the methylene group plays an important role in the down-regulation of c-FLIP and Mcl-1 proteins and apoptosis induction which is inactivated by GSTP1-1 through forming GSH conjugates.

[728]

TÍTULO / TITLE: - Transglutaminase 2 expression predicts progression free survival in non-small cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Korean Med Sci. 2013 Jul;28(7):1005-14. doi: 10.3346/jkms.2013.28.7.1005. Epub 2013 Jul 3.

●● Enlace al texto completo (gratis o de pago) [3346/jkms.2013.28.7.1005](#)

AUTORES / AUTHORS: - Jeong JH; Cho BC; Shim HS; Kim HR; Lim SM; Kim SK; Chung KY; Islam SM; Song JJ; Kim SY; Kim JH

INSTITUCIÓN / INSTITUTION: - Yonsei University Graduate School of Medicine, Yonsei University College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - Transglutaminase 2 (TG2), a cross-linking enzyme, is involved in drug resistance and in the constitutive activation of nuclear factor kappa B (NF-kappaB). We investigated the association of non-small cell lung cancer (NSCLC) treatment efficacy with TG2 and NF-kappaB expression in 120 patients: 102 with adenocarcinoma and 18 with other histologic types. All patients underwent surgery; 88 received adjuvant chemotherapy, with 28 receiving platinum-based doublet chemotherapy as first-line treatment and 29 receiving epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy. Patients' TG2 and NF-kappaB expression values were calculated semiquantitatively. The median TG2 value was 50 (range, 0-300) and the median NF-kappaB value was 20 (range, 0-240). Disease-free survival did not differ between the low- and high-TG2 groups. Among patients who received palliative platinum-based doublet chemotherapy, progression free survival (PFS) was longer in the low-TG2 group than in the high-TG2 group (11.0 vs. 7.0 months; P=0.330). Among those who received EGFR-TKI therapy, PFS was also longer in the low-TG2 group than in the high-TG 2 group (11.0 vs. 2.0 months; P=0.013). Similarly, in EGFR wild-type patients treated with EGFR-TKI, PFS was longer in patients with low TG2 expression (9.0 vs. 2.0 months; P=0.013). TG2 expression levels can predict PFS in patients with NSCLC treated with EGFR-TKI.

[729]

TÍTULO / TITLE: - Sodium selenite induces apoptosis in colon cancer cells via Bax-dependent mitochondrial pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur Rev Med Pharmacol Sci. 2013 Aug;17(16):2166-71.

AUTORES / AUTHORS: - Li Z; Meng J; Xu TJ; Qin XY; Zhou XD

INSTITUCIÓN / INSTITUTION: - Department of Ultrasound, Xijing Hospital, The Fourth Military Medical University, Xi'an Shanxi, P.R. China.

zhouxiaodong2013@hotmail.com

RESUMEN / SUMMARY: - **OBJECTIVES:** We aimed to elucidate a possible mechanism of action by investigating the effects of selenium (Se) on cell cycle arrest and apoptosis in colorectal cancer cells (HCT116 cells and SW620 cells). **MATERIALS AND METHODS:** The colorectal cancer cells were treated with varying concentrations of Se (1 microM, 5 microM and 10 microM) for 24 hours. The effects of Se on cell cycle, apoptosis, mitochondrial transmembrane potential and apoptosis related proteins were examined by flow cytometry assessment and immunoblotting. **RESULTS:** Se induced G2/M cell cycle arrest and apoptosis in colorectal cancer cells (HCT116 cells and SW620 cells) in a dose-dependent manner. Bax (Bcl2 associated X protein) was up-regulated and Bcl-2 (B cell lymphoma gene-2) was down-regulated after Se treatment in both cells in a dose-dependent manner. Se caused increased loss of MMP (matrix metalloproteinase) and induced Bax translocation from cytosol into

mitochondria and caspase 3 activation in both colorectal cancer cells in a dose-dependent manner. CONCLUSIONS: Se induced G2/M cell cycle arrest and apoptosis in both colorectal cancer cells via Bax-dependent mitochondrial pathway.

[730]

TÍTULO / TITLE: - Flavokawain B, a kava chalcone, inhibits growth of human osteosarcoma cells through G2/M cell cycle arrest and apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer. 2013 Jun 10;12:55. doi: 10.1186/1476-4598-12-55.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1476-4598-12-55](#)

AUTORES / AUTHORS: - Ji T; Lin C; Krill LS; Eskander R; Guo Y; Zi X; Hoang BH

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedic Surgery, UC Irvine Multidisciplinary Sarcoma Center, Chao Family Comprehensive Cancer Center, University of California, Irvine, USA.

RESUMEN / SUMMARY: - BACKGROUND: Osteosarcoma (OS) is the most common primary bone malignancy with a high propensity for local invasion and distant metastasis. Limited by the severe toxicity of conventional agents, the therapeutic bottleneck of osteosarcoma still remains unconquered. Flavokawain B (FKB), a kava extract, has been reported to have significant anti-tumor effects on several carcinoma cell lines both in vitro and in vivo. Its efficacy and low toxicity profile make FKB a promising agent for use as a novel chemotherapeutic agent. RESULTS: In the current study, we investigated the anti-proliferative and apoptotic effects of FKB against human osteosarcomas. Exposure of OS cells to FKB resulted in apoptosis, evidenced by loss of cell viability, morphological changes and the externalization of phosphatidylserine. Apoptosis induced by FKB resulted in activation of Caspase-3/7, -8 and -9 in OS cell lines, 143B and Saos-2. FKB also down-regulated inhibitory apoptotic markers, including Bcl-2 and Survivin and led to concomitant increases in apoptotic proteins, Bax, Puma and Fas. Therefore, the induction of apoptosis by FKB involved both extrinsic and intrinsic pathways. FKB also caused G2/M phase cell cycle arrest, which was observed through reductions in the levels of cyclin B1, cdc2 and cdc25c and increases in Myt1 levels. Furthermore, migration and invasion ability was decreased by FKB in a dose-dependent manner. The cytotoxicity profile showed FKB had significant lower side effects on bone marrow cells and small intestinal epithelial cells compared with Adriamycin. CONCLUSIONS: Taken together, our evidence of apoptosis and cell cycle arrest by FKB treatment with less toxicity than the standard treatments provides an innovative argument for the use of FKB as a chemotherapeutic and chemopreventive compound. In vivo experiments utilizing FKB to reduce tumorigenesis and metastatic potential will be crucial to further justify clinical application.

[731]

TÍTULO / TITLE: - Surfactin-Induced Apoptosis Through ROS-ERS-Ca-ERK Pathways in HepG2 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Jun 4.

●● Enlace al texto completo (gratis o de pago) [1007/s12013-013-9676-](#)

[7](#)

AUTORES / AUTHORS: - Wang CL; Liu C; Niu LL; Wang LR; Hou LH; Cao XH

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Food Nutrition and Safety, Tianjin University of Science & Technology, Ministry of Education, No. 29, 13th Avenue, Tianjin Economy Technological Development Area, Tianjin, 300457, China, wangchunling@tust.edu.cn.

RESUMEN / SUMMARY: - Although surfactin is able to inhibit cancer cell proliferation and to induce cancer cell apoptosis, the molecular mechanism responsible for this process remain elusive. In this study, the signaling network underlying the apoptosis of human hepatoma (HepG2) cells induced by surfactin was investigated. It is found that the reaction oxygen species (ROS) production and intracellular calcium ([Ca²⁺]_i) accumulation are both induced HepG2 cells apoptosis. The [Ca²⁺]_i exaltation was partly depended on the Ca²⁺ release from inositol 1,4,5-trisphosphate (IP₃) and ryanodine (Ry) receptors channels, which both triggered endoplasmic reticulum stress (ERS). The results showed that surfactin induced the ROS production and ROS production led to ERS. The occurrence of ERS increased the [Ca²⁺]_i level and the processes associated with blocking extracellular signal-regulated kinase (ERK) pathway. According to a comprehensive review of all the evidence, it is concluded that surfactin induces apoptosis of HepG2 cells through a ROS-ERS-Ca²⁺ mediated ERK pathway.

[732]

TÍTULO / TITLE: - JNK activation is required for TNFalpha-induced apoptosis in human hepatocarcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int Immunopharmacol. 2013 Sep;17(1):92-8. doi: 10.1016/j.intimp.2013.05.017. Epub 2013 Jun 7.

●● Enlace al texto completo (gratis o de pago)

[1016/j.intimp.2013.05.017](#)

AUTORES / AUTHORS: - Minero VG; Khadjavi A; Costelli P; Baccino FM; Bonelli G

INSTITUCIÓN / INSTITUTION: - Department of Experimental Medicine and Oncology, University of Turin, Italy; Department of Molecular Biotechnology and Health Sciences, University of Turin, Italy.

RESUMEN / SUMMARY: - BACKGROUND: A frequent distinctive feature of tumors, hepatocellular carcinomas included, is resistance to apoptosis induced by a variety of agents, among which the pleiotropic cytokine tumor necrosis factor-alpha (TNF). Compared to other cell types, hepatocytes and hepatoma-derived cell lines are poorly susceptible to TNF-induced apoptosis, which is largely ascribed to activation of the prosurvival transcription factor NF-kappaB and can be overcome by associating TNF to low doses of protein synthesis inhibitors or other drugs. AIMS: This study analyses the molecular mechanisms by which TNF, in combination with cycloheximide (CHX), induces apoptosis in human hepatoma-derived Huh7 cells, focusing on the role played by JNK. METHODS: Huh7 cell cultures were treated with TNF+CHX in the presence or in the absence of the pancaspase inhibitor zVADfmk or of the JNK inhibitor SP600125 as well as after suppression of JNK expression by RNAi. Apoptosis was assessed both by light microscopy and by flow cytometry, JNK and caspase activation by western blotting and/or enzymatic assay. RESULTS: TNF+CHX-induced death of Huh7 cells involved JNK activation since it was partially prevented by suppressing JNK activity or expression. Moreover, apoptosis was significantly reduced also by zVADfmk, while SP600125 and zVADfmk combined totally abrogated cell death in an additive fashion. CONCLUSIONS: These results demonstrate a causal role for JNK and caspases in TNF+CHX-induced apoptosis of Huh7 human hepatoma cells. Therefore, strategies aimed at enhancing both pathways should provide a profitable basis to overcome the resistance of hepatocarcinoma cells to TNF-dependent apoptosis.

[733]

TÍTULO / TITLE: - Profilin1 sensitizes pancreatic cancer cells to irradiation by inducing apoptosis and reducing autophagy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Curr Mol Med. 2013 Jun 28.

AUTORES / AUTHORS: - Cheng H; Li J; Liu C; Yao W; Xu Y; Frank TS; Cai X; Shi S; Lu Y; Qin Y; Liu L; Xu J; Long J; Ni QX; Li M; Yu X

INSTITUCIÓN / INSTITUTION: - The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School at Houston, Houston, Texas 77030, USA. Min.Li@uth.tmc.edu.

RESUMEN / SUMMARY: - Pancreatic cancer has an extremely poor prognosis mainly due to lack of effective treatment options. Radiotherapy is mostly applied to locally advanced cases, although tumor radioresistance limits the effectiveness. Profilin1, a novel tumor suppressor gene, was reported to be down-regulated in various cancers and associated with tumor progression. The objective of this study was to demonstrate how profilin1 affected pancreatic cancer radiosensitivity. We showed profilin1 was down-regulated in pancreatic cancer cells after exposure to radiation, and re-expression of profilin1

suppressed tumor cell viability and increased DNA damage following irradiation. Further studies revealed that up-regulation of profilin1 facilitated apoptosis and repressed autophagy induced by irradiation, which might sensitize pancreatic cancer cells to radiation treatment. Our findings may provide a novel therapeutic strategy for sensitizing pancreatic cancer to radiotherapy.

[734]

TÍTULO / TITLE: - Downregulation of CD24 inhibits invasive growth, facilitates apoptosis and enhances chemosensitivity in gastric cancer AGS cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur Rev Med Pharmacol Sci. 2013 Jul;17(13):1709-15.

AUTORES / AUTHORS: - Jiao XL; Zhao C; Niu M; Chen D

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, Ultrasound and Pharmacy, The Affiliated Hospital of Medical College, Qingdao University, Qingdao, Shandong, R.P. China. chendd820@126.com.

RESUMEN / SUMMARY: - BACKGROUND AND AIM: The human CD24 antigen is a small heavily glycosylated cell surface protein, which is expressed in a large variety of solid tumors, including gastric cancer. Enriched on the surface of many tumor cells, CD24 promotes tumor growth, invasion and metastasis and confers resistance to some chemotherapeutic drugs. In this study, we investigated the possible effect of CD24 suppression on proliferation, apoptosis, migration, invasion and chemosensitivity of gastric cancer (GC) cells.

MATERIALS AND METHODS: We down-regulated CD24 expression by RNA interference and investigated the effects on proliferation, apoptosis, chemosensitivity to doxorubicin, malignant and metastatic potential of a human gastric cancer cell line, AGS, CD24-suppressed clones, AGS-CD24-siRNA-C2, AGS-CD24-siRNA-C4 and AGS-CD24-siRNA-C5 in vitro. We evaluated the effects of CD24 suppression in vivo on xenograft tumor growth and metastatic properties following tail iv AGS-CD24-siRNA-C2, AGS-CD24-siRNA-C4 and AGS-CD24-siRNA-C5 clones. We also investigated the effect of CD24-siRNA followed by doxorubicin administration treatment on the xenograft tumor growth.

RESULTS: CD24 suppressed showed significantly decreased proliferation, invasion and increased apoptosis as well as increased chemosensitivity to doxorubicin in vitro and in vivo.

CONCLUSIONS: CD24 involves in proliferation, invasion and chemosensitivity of human gastric cancer cell line AGS, and that down-regulation of CD24 protein expression decreases the metastatic potential and increases chemosensitivity of gastric cancer (GC) cells. Thus, CD24 may be a promising therapeutic target for gastric cancer.

[735]

TÍTULO / TITLE: - Induction of apoptosis by high-dose gold nanoparticles in nasopharyngeal carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Auris Nasus Larynx. 2013 May 27. pii: S0385-8146(13)00118-1. doi: 10.1016/j.anl.2013.04.011.

●● Enlace al texto completo (gratis o de pago) [1016/j.anl.2013.04.011](#)

AUTORES / AUTHORS: - Lan MY; Hsu YB; Hsu CH; Ho CY; Lin JC; Lee SW

INSTITUCIÓN / INSTITUTION: - Department of Otolaryngology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC.

RESUMEN / SUMMARY: - OBJECTIVE: Nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world, but is a common cancer in southern Asia. Local recurrent disease and distant metastasis of NPC are still the unsolved problems. Recently, gold nanoparticles (AuNPs) have been developed as potential in vivo diagnostic and therapeutic agents. However, their role on nasopharyngeal cancer remains unknown. The object of this study is to investigate if AuNPs can be used as a new therapeutic agent for NPC by evaluating their anti-tumor effect in vitro. METHODS: The AuNPs were prepared by the reduction of chloroauric acid to neutral gold. Their size distribution and microstructures were characterized by transmission electron microscopy (TEM). To evaluate their cytotoxic effect, NPC cell line TW01 and Human Nasal Epithelial Cells (HNEpC) were cultured in various concentrations of AuNPs for 3 days. Cell viability was evaluated by Trypan Blue viability assay while morphologic findings were observed via light microscopy. Terminal deoxynucleotidyltransferase-mediated dUPT nick end labeling (TUNEL) assay was used to detect apoptosis. RESULTS: AuNPs prepared in this study had an average diameter of 20.5nm and they were observed under light microscopy as dark material aggregated in the cells after treatment. Contrary to the HNEpC, the AuNPs reduced cell viability of NPC cell in a concentration-dependant manner by Trypan Blue assay, especially at high concentration. Besides, cell apoptosis was demonstrated by positive TUNEL assay. CONCLUSIONS: The AuNP possesses specific imaging properties and is cytotoxic to NPC cells at high concentrations.

[736]

TÍTULO / TITLE: - Phenethyl isothiocyanate triggers apoptosis in human malignant melanoma A375.S2 cells through reactive oxygen species and the mitochondria-dependent pathways.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hum Exp Toxicol. 2013 Jun 11.

●● Enlace al texto completo (gratis o de pago)

[1177/0960327113491508](#)

AUTORES / AUTHORS: - Huang SH; Hsu MH; Hsu SC; Yang JS; Huang WW; Huang AC; Hsiao YP; Yu CC; Chung JG

INSTITUCIÓN / INSTITUTION: - 1Department of Biotechnology, Asia University, Taichung, Taiwan.

RESUMEN / SUMMARY: - We have reported previously that phenethyl isothiocyanate (PEITC) induces apoptosis in human osteosarcoma U-2 OS cells. Cytotoxic activity of PEITC towards other cancer cells such as human malignant melanoma and skin cancer cells has not been reported. In this study, the anticancer activity of PEITC towards human malignant melanoma cancer A375.S2 cells was investigated. To determine the mechanisms of PEITC inhibition of cell growth, the following end points were determined in A375.S2 cells: cell morphological changes, cell cycle arrest, DNA damage and fragmentation assays and morphological assessment of nuclear change, reactive oxygen species (ROS) and Ca²⁺ generations, mitochondrial membrane potential disruption, and nitric oxide and 10-N-nonyl acridine orange productions, expression and activation of caspase-3 and -9, B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax), Bcl-2, poly (adenosine diphosphate-ribose) polymerase, and cytochrome c release, apoptosis-inducing factor and endonuclease G. PEITC induced morphological changes in time- and dose-dependent manner. PEITC induced G2/M phase arrest and induced apoptosis via endoplasmic reticulum stress-mediated mitochondria-dependent pathway. Western blot analysis showed that PEITC promoted Bax expression and inhibited Bcl-2 expression associated with the disintegration of the outer mitochondrial membrane causing cytochrome c release, and activation of caspase-9 and -3 cascade leading to apoptosis. We conclude that PEITC-triggered apoptotic death in A375.S2 cells occurs through ROS-mediated mitochondria-dependent pathways.

[737]

TÍTULO / TITLE: - ATF2 knockdown reinforces oxidative stress-induced apoptosis in TE7 cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cell Mol Med. 2013 Jun 25. doi: 10.1111/jcmm.12071.

●● Enlace al texto completo (gratis o de pago) 1111/jcmm.12071

AUTORES / AUTHORS: - Walluscheck D; Poehlmann A; Hartig R; Lendeckel U; Schonfeld P; Hotz-Wagenblatt A; Reissig K; Bajbouj K; Roessner A; Schneider-Stock R

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Otto-von-Guericke University, Magdeburg, Germany.

RESUMEN / SUMMARY: - Cancer cells showing low apoptotic effects following oxidative stress-induced DNA damage are mainly affected by growth arrest. Thus, recent studies focus on improving anti-cancer therapies by increasing apoptosis sensitivity. We aimed at identifying a universal molecule as potential target to enhance oxidative stress-based anti-cancer therapy through a switch from cell cycle arrest to apoptosis. A cDNA microarray was performed with

hydrogen peroxide-treated oesophageal squamous epithelial cancer cells TE7. This cell line showed checkpoint activation via p21WAF1, but low apoptotic response following DNA damage. The potential target molecule was chosen depended on the following demands: it should regulate DNA damage response, cell cycle and apoptosis. As the transcription factor ATF2 is implicated in all these processes, we focused on this protein. We investigated checkpoint activation via ATF2. Indeed, ATF2 knockdown revealed ATF2-triggered p21WAF1 protein expression, suggesting p21WAF1 transactivation through ATF2. Using chromatin immunoprecipitation (ChIP), we identified a hitherto unknown ATF2-binding sequence in the p21WAF1 promoter. p-ATF2 was found to interact with p-c-Jun, creating the AP-1 complex. Moreover, ATF2 knockdown led to c-Jun downregulation. This suggests ATF2-driven induction of c-Jun expression, thereby enhancing ATF2 transcriptional activity via c-Jun-ATF2 heterodimerization. Notably, downregulation of ATF2 caused a switch from cell cycle arrest to reinforced apoptosis, presumably via p21WAF1 downregulation, confirming the importance of ATF2 in the establishment of cell cycle arrest. 1-Chloro-2,4-dinitrobenzene also led to ATF2-dependent G2/M arrest, suggesting that this is a general feature induced by oxidative stress. As ATF2 knockdown also increased apoptosis, we propose ATF2 as a target for combined oxidative stress-based anti-cancer therapies.

[738]

TÍTULO / TITLE: - Endoplasmic reticulum stress-mediated apoptosis in imatinib-resistant leukemic K562-r cells triggered by AMN107 combined with arsenic trioxide.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Exp Biol Med (Maywood). 2013 Jul 24.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1177/1535370213492689](#)

AUTORES / AUTHORS: - Xia Y; Fang H; Zhang J; Du Y

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Stem Cell Biology, Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) and Shanghai Jiao Tong University School of Medicine (SJTU-SM), Shanghai 200025, China.

RESUMEN / SUMMARY: - The first tyrosine kinase inhibitor (TKI) imatinib mesylate (imatinib) targets the kinase domain of BCR-ABL and induces apoptosis in newly diagnosed chronic myeloid leukaemia (CML). However, resistant and relapse are common problems in imatinib-treated patients. Although second-generation TKI such as AMN107 appears to improve the treatment of CML, TKI resistance and relapse are also frequently occurred in the patients. To test whether arsenic trioxide (ATO) could potentiate the efficacy of AMN107 in imatinib-resistant cells, we conducted a series of assays in TKI-resistant K562-r cells treated with AMN107 and ATO. Based on a time-course

cDNA microarray analysis, we found many genes typically involved in the endoplasmic reticulum (ER) stress signalling were significantly up-regulated, implicating the occurrence of ER stress-mediated apoptosis in K562-r cells treated with the combination of ATO and AMN107. Such implication was also supported by the data showing the activation of members in the JNK pathway, which are known to be characteristic markers bridging ER-stress and apoptosis. Partial knock-down of the JNK activities alleviated the effects of apoptosis ($p < 0.05$) triggered by combining AMN107 with ATO. In conclusion, this study for the first time demonstrates a synergistic effect of AMN107 with ATO, allowing insights into the possible mechanisms underlying imatinib-induced resistance in CML. Our data also suggest that combination of AMN107 with ATO may represent a new strategy for the treatment of imatinib-resistant CML patients.

[739]

TÍTULO / TITLE: - Sodium nitroprusside (SNP) sensitizes human gastric cancer cells to TRAIL-induced apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int Immunopharmacol. 2013 Jul 16;17(2):383-389. doi: 10.1016/j.intimp.2013.06.021.

- Enlace al texto completo (gratis o de pago)

1016/j.intimp.2013.06.021

AUTORES / AUTHORS: - Yang L; Lan C; Fang Y; Zhang Y; Wang J; Guo J; Wan S; Yang S; Wang R; Fang D

INSTITUCIÓN / INSTITUTION: - Department of Gastroenterology, Southwest Hospital, Third Military Medical University, Chongqing 400038, China.

RESUMEN / SUMMARY: - AIM: To investigate the effects of the nitrous oxide (NO)-donor sodium nitroprusside (SNP) on tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in human gastric cancer cells. METHODS: The MTT assay and flow cytometry were used to detect cellular proliferation and markers of apoptosis, respectively. Expression levels of caspases-8, and 9 were determined by Western blot. Changes in Nitric Oxide Synthase (NOS) activity, NO production, and caspase activation were also evaluated. RESULTS: We found that TRAIL induced apoptosis and cell cycle arrest in human gastric cancer cell lines, and that this effect was mediated by NO production, and activation of both the extrinsic and intrinsic signaling pathways of apoptosis. In addition, we found that the NO-donor SNP sensitizes gastric cancer cells to TRAIL-mediated apoptosis. Treatment of cells with both TRAIL and SNP resulted in increased activation of caspase-8 and caspase-9 and NO release. Inhibition of caspase-8 blocked cell TRAIL-induced apoptosis, while a selective caspase-9 inhibitor was unable to prevent apoptosis induced by either TRAIL or TRAIL plus SNP. Inhibition of NOS could block the activation of caspase-9, but had no obvious effect on cell apoptosis. CONCLUSIONS: SNP-sensitized gastric cancer cells to TRAIL-induced cytotoxicity by stimulating

the release of NO, in turn facilitating the mitochondria-mediated signal transduction pathway. The engagement of the mitochondria signaling pathways along with the TRAIL death receptor signaling pathway synergistically increase levels of apoptosis in these cells.

[740]

TÍTULO / TITLE: - BCR-ABL1 RT-qPCR for Monitoring the Molecular Response to Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Diagn. 2013 Jun 27. pii: S1525-1578(13)00100-1. doi: 10.1016/j.jmoldx.2013.04.007.

●● Enlace al texto completo (gratis o de pago)

[1016/j.jmoldx.2013.04.007](#)

AUTORES / AUTHORS: - Press RD; Kamel-Reid S; Ang D

INSTITUCIÓN / INSTITUTION: - Department of Pathology and Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, Canada. Electronic address: pressr@ohsu.edu.

RESUMEN / SUMMARY: - The pathognomonic genetic alteration in chronic myeloid leukemia is the formation of the BCR-ABL1 fusion gene, which produces a constitutively active tyrosine kinase that drives leukemic transformation. Targeted tyrosine kinase inhibitor treatment with imatinib, nilotinib, dasatinib, bosutinib, and ponatinib is the cornerstone of modern therapy for this hematologic malignancy. Real-time quantitative RT-PCR (RT-qPCR) of BCR-ABL1 RNA is a necessary laboratory technique for monitoring the efficacy of tyrosine kinase inhibitor therapy and quantitatively assessing minimal residual disease. The molecular response measured by BCR-ABL1 RT-qPCR assists in identifying suboptimal responses and can help inform the decision to switch to alternative therapies that may be more efficacious (or to pursue more stringent monitoring). Furthermore, the tyrosine kinase inhibitor-mediated molecular response provides valuable risk stratification and prognostic information on long-term outcomes. Despite these attributes, informed, universal, practical utilization of this well-established monitoring test will require heightened efforts by the molecular diagnostics laboratory community to adopt the standardized reporting units of the International Scale. Without widespread adoption of the International Scale, the consensus major molecular response and early molecular response treatment thresholds will not be definable, and optimal clinical outcomes for patients with chronic myeloid leukemia may not be achieved.

[741]

TÍTULO / TITLE: - Cyclin G1 Expands Liver Tumor-Initiating Cells by Sox2 Induction via Akt/mTOR Signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0099](#)

AUTORES / AUTHORS: - Wen W; Han T; Chen C; Huang L; Sun W; Wang X; Chen SZ; Xiang DM; Tang L; Cao D; Feng GS; Wu MC; Ding J; Wang HY

INSTITUCIÓN / INSTITUTION: - 1International Cooperation Laboratory on, Eastern Hepatobiliary Surgery Institute.

RESUMEN / SUMMARY: - Recurrence and chemo-resistance of liver cancer has been attributed to the existence of liver tumor-initiating cells (T-ICs). It is important to decipher the molecular mechanism for acquisition of drug-resistance and to design combinatorial therapeutic strategies. Cyclin G1 has been shown to play a pivotal role in initiation and metastasis of HCC. In this study, we found that enhanced cyclin G1 expression was associated with drug resistance of hepatoma cells and higher recurrence rate of HCC patients. Expression of cyclin G1 was elevated in liver T-ICs and closely correlated with the expression of liver T-IC markers. Forced cyclin G1 expression remarkably enhanced self-renewal and tumorigenicity of hepatoma cells. Cyclin G1 overexpression dramatically up-regulated the expression of Sox2 both in vitro and in vivo, which was impaired by chemical inhibitors of Akt/mTOR signaling. Furthermore, blockade of Akt/mTOR signaling or interference of Sox2 expression suppressed cyclin G1-enhanced self-renewal, chemo-resistance and tumorigenicity of hepatoma cells, indicating that cyclin G1 expands liver T-ICs through sox2 induction via Akt/mTOR signaling pathway. These results suggest that Cyclin G1-induced liver T-IC expansion contributes to the recurrence and chemo-resistance of hepatoma, and cyclin G1 may be a promising biomarker for individualized therapy of HCC patients.

[742]

TÍTULO / TITLE: - Evaluation of multiple myeloma cell apoptosis in primary bone marrow samples.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lab. 2013;59(3-4):389-95.

AUTORES / AUTHORS: - Rebersek K; Cernelc P; Podgornik H

INSTITUCIÓN / INSTITUTION: - Department of Haematology, University Medical Centre Ljubljana, Zaloška 7, 1505 Ljubljana, Slovenia.

RESUMEN / SUMMARY: - BACKGROUND: Although different approaches have been proposed to selectively determine multiple myeloma (MM) cells in a heterogeneous population of bone marrow (BM) cells, studies on plasma cells from primary samples of MM patients are still challenging. This is partially due to difficulties in obtaining a suitable amount of sample, but even more due to uneven infiltration of BM by MM cells. When the apoptotic effect of different agents on MM plasma cells is studied, evaluation is additionally complicated by

morphological changes induced by apoptosis. We introduce a modified gating approach combining specific antibodies and exclusion of cellular interferences. **METHODS:** The extent of apoptosis induced by arsenic trioxide and camptothecin was evaluated by flow cytometry using annexin V and propidium iodide (PI) after selective labelling of plasma cells with CD38 and CD138 antibodies. We selectively analysed MM plasma cell apoptosis combining CD38/CD138-positivity and exclusion of cellular interferences. **RESULTS:** Thirty BM samples from newly diagnosed MM patients were analysed. We compared the proportion of cells in different phases of apoptosis obtained by gating on a CD38/CD138-positive population only and by the novel approach. The proportion of cells in early apoptosis evaluated by the modified gating technique was significantly higher for both inductors. **CONCLUSIONS:** The introduced gating approach can increase the reliability of selective evaluation of MM plasma cell apoptosis in primary samples. The modified method can further be implemented for the analysis of various processes in plasma cells by flow cytometry.

[743]

TÍTULO / TITLE: - Germline pharmacogenetics of paclitaxel for cancer treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Jul;14(9):1065-84. doi: 10.2217/pgs.13.90.

- Enlace al texto completo (gratis o de pago) [2217/pgs.13.90](#)

AUTORES / AUTHORS: - Hertz DL

INSTITUCIÓN / INSTITUTION: - Department of Clinical, Social, & Administrative Sciences, University of Michigan College of Pharmacy, Ann Arbor, MI, USA. DLHertz@med.umich.edu.

RESUMEN / SUMMARY: - Paclitaxel is a highly effective chemotherapeutic agent used in a variety of solid tumors. Some paclitaxel-treated patients experience the intended therapeutic response with manageable side effects, while others have minimal response and/or severe toxicity. This variability in treatment outcome is partially determined by variability in drug exposure (pharmacokinetics) and by patient and tumor sensitivity (pharmacodynamics). Both pharmacokinetics and pharmacodynamics are dictated in part by common variants in the germline genome, known as SNPs. This article reviews the published literature on paclitaxel pharmacogenetics in cancer, focusing primarily on polymorphisms in genes relevant to paclitaxel pharmacokinetics and discusses preliminary work on pharmacodynamic genes and genome-wide association studies.

[744]

TÍTULO / TITLE: - Combination treatment of PD98059 and DAPT in gastric cancer through induction of apoptosis and downregulation of WNT/beta-catenin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 14;14(9).

AUTORES / AUTHORS: - Yao J; Qian C; Shu T; Zhang X; Zhao Z; Liang Y

INSTITUCIÓN / INSTITUTION: - Institute of Medical Cell Biology; School of Medicine; Taizhou University; Taizhou, Zhejiang, China.

RESUMEN / SUMMARY: - gamma-secretase inhibitors (GSIs), the indirect inhibitors of Notch, are emerging as a new class of anticancer agents for the treatment of solid and hematological malignancies, but little is known about their effects on gastric cancer. In this study, we demonstrate that DAPT, a potent GSI, was effective to inhibit gamma-secretase activity in gastric cancer (GC) cell lines which contained a fragment with approximately the size of the Notch1 intracellular domain (NICD), but was limited in their ability to induce apoptosis. However, activation of extracellular signal-regulated kinase (ERK)1/2 upon DAPT treatment was detected. Selective inhibition of ERK1/2 activation dramatically sensitized GC cells to apoptosis via downregulating beta-catenin signaling in these GC cells. Notably, in a xenograft mouse tumor model, combination therapy using ERK inhibitor PD98059 plus DAPT yielded additive antitumor effects as compared with either agent alone. Taken together, these data demonstrated that gamma-secretase inhibition combined with ERK1/2 inhibitor enhances cell death in GC cells partly through downregulation of WNT/beta-catenin pathways.

[745]

TÍTULO / TITLE: - Epigenetic-mediated tumor suppressor genes as diagnostic or prognostic biomarkers in gastric cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Rev Mol Diagn. 2013 Jun;13(5):445-55. doi: 10.1586/erm.13.32.

●● Enlace al texto completo (gratis o de pago) [1586/erm.13.32](#)

AUTORES / AUTHORS: - Otani K; Li X; Arakawa T; Chan FK; Yu J

INSTITUCIÓN / INSTITUTION: - Department of Medicine and Therapeutics, Institute of Digestive Disease, Li KaShing Institute of Health Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong. junyu@cuhk.edu.hk.

RESUMEN / SUMMARY: - Gastric cancer is believed to result in part from the accumulation of multiple genetic and epigenetic alterations leading to oncogene overexpression and tumor suppressor loss. Tumor suppressor genes are inactivated more frequently by promoter methylation than by mutation in gastric cancer. Identification of genes inactivated by promoter methylation is a powerful approach to discover novel tumor suppressor genes. We have previously identified tumor suppressor genes in gastric cancer by genome-wide

methylation screening. The biological functions of these genes are related to cell adhesion, ubiquitination, transcription, p53 regulation and diverse signaling pathways. Some of the tumor suppressor genes are of particular clinical importance as they can be used as predictive biomarkers for early diagnosis or ongoing prognosis of gastric cancer.

[746]

TÍTULO / TITLE: - CDC25A protein stability represents a previously unrecognized target of HER2 signaling in human breast cancer: implication for a potential clinical relevance in trastuzumab treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neoplasia. 2013 Jun;15(6):579-90.

AUTORES / AUTHORS: - Brunetto E; Ferrara AM; Rampoldi F; Talarico A; Cin ED; Grassini G; Spagnuolo L; Sassi I; Ferro A; Cuorvo LV; Barbareschi M; Piccinin S; Maestro R; Pecciarini L; Doglioni C; Cangi MG

INSTITUCIÓN / INSTITUTION: - Pathology Unit, San Raffaele Scientific Institute, Milano, Italy.

RESUMEN / SUMMARY: - The CDC25A-CDK2 pathway has been proposed as critical for the oncogenic action of human epidermal growth factor receptor 2 (HER2) in mammary epithelial cells. In particular, transgenic expression of CDC25A cooperates with HER2 in promoting mammary tumors, whereas CDC25A hemizygous loss attenuates the HER2-induced tumorigenesis penetrance. On the basis of this evidence of a synergism between HER2 and the cell cycle regulator CDC25A in a mouse model of mammary tumorigenesis, we investigated the role of CDC25A in human HER2-positive breast cancer and its possible implications in therapeutic response. HER2 status and CDC25A expression were assessed in 313 breast cancer patients and we found statistically significant correlation between HER2 and CDC25A ($P = .007$). Moreover, an HER2-positive breast cancer subgroup with high levels of CDC25A and very aggressive phenotype was identified ($P = .005$). Importantly, our in vitro studies on breast cancer cell lines showed that the HER2 inhibitor efficacy on cell growth and viability relied also on CDC25A expression and that such inhibition induces CDC25A down-regulation through phosphatidylinositol 3-kinase/protein kinase B pathway and DNA damage response activation. In line with this observation, we found a statistical significant association between CDC25A overexpression and trastuzumab-combined therapy response rate in two different HER2-positive cohorts of trastuzumab-treated patients in either metastatic or neoadjuvant setting ($P = .018$ for the metastatic cohort and $P = .021$ for the neoadjuvant cohort). Our findings highlight a link between HER2 and CDC25A that positively modulates HER2-targeted therapy response, suggesting that, in HER2-positive breast cancer patients, CDC25A overexpression affects trastuzumab sensitivity.

[747]

TÍTULO / TITLE: - Erratum to: MGMT methylation analysis of glioblastoma on the Infinium methylation BeadChip identifies two distinct CpG regions associated with gene silencing and outcome, yielding a prediction model for comparisons across datasets, tumor grades, and CIMP-status.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Neuropathol. 2013 Jul;126(1):159. doi: 10.1007/s00401-013-1134-5. Epub 2013 Jun 8.

●● Enlace al texto completo (gratis o de pago) [1007/s00401-013-1134-](#)

[5](#)

AUTORES / AUTHORS: - Bady P; Sciuscio D; Diserens AC; Bloch J; van den Bent MJ; Marosi C; Dietrich PY; Weller M; Mariani L; Heppner FL; Macdonald DR; Lacombe D; Stupp R; Delorenzi M; Hegi ME

INSTITUCIÓN / INSTITUTION: - Department of Clinical Neurosciences, Lausanne University Hospital, Lausanne, Switzerland.

[748]

TÍTULO / TITLE: - HLA-A2-restricted Cytotoxic T Lymphocyte Epitopes from Human Hepsin as Novel Targets for Prostate Cancer Immunotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Scand J Immunol. 2013 May 31. doi: 10.1111/sji.12083.

●● Enlace al texto completo (gratis o de pago) [1111/sji.12083](#)

AUTORES / AUTHORS: - Guo J; Li G; Tang J; Cao XB; Zhou QY; Fan ZJ; Zhu B; Pan XH

INSTITUCIÓN / INSTITUTION: - The Research Center of Stem Cell, Tissue and Organ Engineering, Kunming General Hospital of PLA, Kunming, 650032, P.R. China.

RESUMEN / SUMMARY: - Hepsin is a type II transmembrane serine protease that is overexpressed in prostate cancer, and it is associated with prostate cancer cellular migration and invasion. Therefore, HPN is a biomarker for prostate cancer. CD8+ T cells play an important role in tumor immunity. The present study predicted and identified HLA-A2-restricted cytotoxic T lymphocyte (CTL) epitopes in human hepsin protein. HLA-A2-restricted CTL epitopes were identified using the following four-step procedure: (1) a computer program generated predicted epitopes from the amino acid sequence of human hepsin; (2) an HLA-A2 binding assay detected the affinity of the predicted epitopes to the HLA-A2 molecule; (3) the primary T-cell response against the predicted epitopes was stimulated in vitro; and (4) the induced CTLs toward different types of hepsin- or HLA-A2-expressing prostate cancer cells were detected. Five candidate peptides were identified. The effectors that were induced by human hepsin epitopes containing residues 229 to 237 (Hpn229; GLQLGVQAV), 268 to 276 (Hpn268; PLTEYIQPV), and 191 to 199 (Hpn199;

SLLSGDWVL) effectively lysed LNCaP prostate cancer cells that were hepsin-positive and HLA-A2 matched. These peptide-specific CTLs did not lyse normal liver cells with low hepsin levels. Hpn229, Hpn268, and Hpn199 increased the frequency of IFN-gamma-producing T cells compared to the negative peptide. These results suggest that the Hpn229, Hpn268, and Hpn199 epitopes are novel HLA-A2-restricted CTL epitopes that are capable of inducing hepsin-specific CTLs in vitro. Hpn229, Hpn268, and Hpn199 peptide-based vaccines may be useful for immunotherapy in patients with prostate cancer. This article is protected by copyright. All rights reserved.

[749]

TÍTULO / TITLE: - Combined Inhibition of HER1/EGFR and RAC1 Results in a Synergistic Antiproliferative Effect on Established and Primary Cultured Human Glioblastoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jul 5.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0052](#)

AUTORES / AUTHORS: - Karpel-Massler G; Westhoff MA; Zhou S; Nonnenmacher L; Dwucet A; Kast RE; Bachem MG; Wirtz CR; Debatin KM; Halatsch ME

INSTITUCIÓN / INSTITUTION: - 1Department of Neurosurgery, University of Ulm.

RESUMEN / SUMMARY: - Glioblastoma is the most frequent brain tumor of glial origin in adults. With the best available standard of care, patients with this disease have a life expectancy of only approximately 15 months after diagnosis. Since the epidermal growth factor receptor (HER1/EGFR) is one of the most commonly dysregulated oncogenes in glioblastoma, HER1/EGFR-targeted agents such as erlotinib were expected to provide a therapeutic benefit. However, their application in the clinical setting failed. Seeking an explanation for this finding, we previously identified several candidate genes for resistance of human glioblastoma cell lines towards erlotinib. Based on this panel of genes, we aimed at identifying drugs that synergistically enhance the antiproliferative effect of erlotinib on established and primary glioblastoma cell lines. We found that NSC23766, an inhibitor of RAC1, enhanced the antineoplastic effects of erlotinib in U87MG, T98MG and A172MG glioblastoma cell lines for the most part in a synergistic or at least in an additive manner. In addition, the synergistic antiproliferative effect of erlotinib and NSC23766 was confirmed in primary cultured cells, indicating a common underlying cellular and molecular mechanism in glioblastoma. Therefore, agents that suppress RAC1 activation may be useful therapeutic partners for erlotinib in a combined targeted treatment for glioblastoma.

[750]

TÍTULO / TITLE: - Erlotinib resistance in EGFR-amplified glioblastoma cells is associated with upregulation of EGFRvIII and PI3Kp110delta

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neuro Oncol. 2013 Jul 21.

●● [Enlace al texto completo \(gratis o de pago\) 1093/neuonc/not093](#)

AUTORES / AUTHORS: - Schulte A; Liffers K; Kathagen A; Riethdorf S; Zapf S; Merlo A; Kolbe K; Westphal M; Lamszus K

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, University Hospital Hamburg-Eppendorf, Hamburg, Germany (A.S., K.L., A.K., S.Z., K.K., M.W., K.L.); Institute for Tumor Biology, University Hospital Hamburg-Eppendorf, Hamburg, Germany (S.R.); Laboratory of Molecular Neuro-Oncology, Department of Clinical and Biological Sciences, University of Basel, Basel, Switzerland (A.M.).

RESUMEN / SUMMARY: - BackgroundThe treatment efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors like erlotinib has not met expectations for glioblastoma therapy, even for EGFR-overexpressing tumors. We determined possible mechanisms of therapy resistance using the unique BS153 glioblastoma cell line, which has retained amplification of the egfr gene and expression of EGFR variant (v)III.MethodsFunctional effects of erlotinib, gefitinib, and cetuximab on BS153 proliferation, migration, and EGFR-dependent signal transduction were systematically compared in vitro. The tumor-initiating capacity of parental and treatment-resistant BS153 was studied in Naval Medical Research Institute/Foxn1nu mice. Potential mediators of resistance were knocked down using small interfering (si)RNA.ResultsErlotinib and gefitinib inhibited proliferation and migration of BS153 in a dose-dependent manner, whereas cetuximab had no effect. BS153 developed resistance to erlotinib (BS153resE) but not to gefitinib. Resistance was associated with strong upregulation of EGFRvIII and subsequent activation of the phosphatidylinositol-3-OH kinase (PI3K) pathway in BS153resE and an increased expression of the regulatory 110-kDa delta subunit of PI3K (p110delta). Knockdown of EGFRvIII in BS153resE largely restored sensitivity to erlotinib. Targeting PI3K pharmacologically caused a significant decrease in cell viability, and specifically targeting p110delta by siRNA partially restored erlotinib sensitivity in BS153resE. In vivo, BS153 formed highly invasive tumors with an unusual growth pattern, displaying numerous satellites distant from the initial injection site. Erlotinib resistance led to delayed onset of tumor growth as well as prolonged overall survival of mice without changing tumor morphology.ConclusionsEGFRvIII can mediate resistance to erlotinib in EGFR-amplified glioblastoma via an increase in PI3Kp110delta. Interfering with PI3Kp110delta can restore sensitivity toward the tyrosine kinase inhibitor.

[751]

TÍTULO / TITLE: - Cyclin D1 Downregulation Contributes to Anticancer Effect of Isorhapontigenin on Human Bladder Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Aug 1.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-0922](#)

AUTORES / AUTHORS: - Fang Y; Cao Z; Hou Q; Ma C; Yao C; Li J; Wu XR; Huang C

INSTITUCIÓN / INSTITUTION: - Authors' Affiliations: 1Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, Zhejiang; 2Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; 3Nelson Institute of Environmental Medicine; and 4Departments of Urology and Pathology, New York University, School of Medicine, New York, New York.

RESUMEN / SUMMARY: - Isorhapontigenin (ISO) is a new derivative of stilbene compound that was isolated from the Chinese herb Gnetum Cleistostachyum and has been used for treatment of bladder cancers for centuries. In our current studies, we have explored the potential inhibitory effect and molecular mechanisms underlying isorhapontigenin anticancer effects on anchorage-independent growth of human bladder cancer cell lines. We found that isorhapontigenin showed a significant inhibitory effect on human bladder cancer cell growth and was accompanied with related cell cycle G0-G1 arrest as well as downregulation of cyclin D1 expression at the transcriptional level in UMUC3 and RT112 cells. Further studies identified that isorhapontigenin downregulated cyclin D1 gene transcription via inhibition of specific protein 1 (SP1) transactivation. Moreover, ectopic expression of GFP-cyclin D1 rendered UMUC3 cells resistant to induction of cell-cycle G0-G1 arrest and inhibition of cancer cell anchorage-independent growth by isorhapontigenin treatment. Together, our studies show that isorhapontigenin is an active compound that mediates Gnetum Cleistostachyum's induction of cell-cycle G0-G1 arrest and inhibition of cancer cell anchorage-independent growth through downregulating SP1/cyclin D1 axis in bladder cancer cells. Our studies provide a novel insight into understanding the anticancer activity of the Chinese herb Gnetum Cleistostachyum and its isolate isorhapontigenin. Mol Cancer Ther; 12(8); 1-12. ©2013 AACR.

[752]

TÍTULO / TITLE: - Visualization of rodent brain tumor angiogenesis and effects of antiangiogenic treatment using 3D DeltaR-muMRA.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Angiogenesis. 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1007/s10456-013-9355-](#)

[8](#)

AUTORES / AUTHORS: - Lin CY; Siow TY; Lin MH; Hsu YH; Tung YY; Jang T; Recht L; Chang C

INSTITUCIÓN / INSTITUTION: - Institute of Biomedical Sciences, Academia Sinica, N123, 128 Sec. 2, Academia Road, Nankang, Taipei, 11529, Taiwan, ROC.

RESUMEN / SUMMARY: - Understanding of structural and functional characteristics of the vascular microenvironment in gliomas and the impact of antiangiogenic treatments is essential for developing better therapeutic strategies. Although a number of methods exist in which this process can be studied experimentally, no single noninvasive test has the capacity to provide information concerning both microvascular function and morphology. The purpose of present study is to demonstrate the feasibility of using a novel three-dimensional DeltaR2-based microscopic magnetic resonance angiography (3D DeltaR2-muMRA) technique for longitudinal imaging of tumor angiogenesis and monitoring the effects of antiangiogenic treatment in rodent brain tumor models. Using 3D DeltaR2-muMRA, a generally consistent early pattern of vascular development in gliomas was revealed, in which a single feeding vessel was visualized first (arteriogenesis), followed by sprouting angiogenesis. Considerable variability of the tumor-associated vasculature was then noted at later stages of tumor evolution. DeltaR2-muMRA revealed that anti-vascular endothelial growth factor treatment induced a rapid and significant alteration of the intratumoral angiogenic phenotype. In summary, 3D DeltaR2-muMRA enables high-resolution visualization of tumor-associated vessels while simultaneously providing functional information on the tumor microvasculature. It can serve as a useful tool for monitoring both the temporal evolution of tumor angiogenesis and the impact of antiangiogenic therapies.

[753]

TÍTULO / TITLE: - Impaired phosphate and tension homologue deleted on chromosome 10 expression and its prognostic role in radical surgery for hepatocellular carcinoma with family aggregation resulting from hepatitis B and liver cirrhosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Exp Biol Med (Maywood). 2013 Jul 4.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1177/1535370213494654](#)

AUTORES / AUTHORS: - Zhong Y; Yan J; Deng M; Hu K; Yao Z; Zou Y; Xu R

INSTITUCIÓN / INSTITUTION: - Department of Hepatobiliary Surgery, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510630, China.

RESUMEN / SUMMARY: - This study aimed to retrospectively investigate the expression of the phosphate and tension homologue deleted on chromosome 10 (PTEN) protein and its prognostic role in hepatocellular carcinoma (HCC) with family aggregation resulting from hepatitis B and liver cirrhosis, which have not been established. Immunohistochemical analysis was performed to evaluate

the PTEN protein expression in HCC and paired para-cancerous tissues from 79 patients with HCC caused by hepatitis B and liver cirrhosis. Of these cases, 34 represented HCC with family aggregation (HCCF group), and 45 represented HCC with no family aggregation (HCCN group). Follow-up data were collected for 3 months to 10 years and analysed for HCC recurrence, survival time and prognostic risk factors. The expression of the PTEN protein in the HCC tissue was dramatically lower in the HCCF group than in the HCCN group. The six-month, one-year and two-year overall recurrence (OR) rates of the HCCF group were significantly higher than those of the HCCN group. The one-year, two-year and five-year overall survival (OS) rates of the HCCF group were lower than those of the HCCN group. Impaired PTEN protein expression was an independent prognostic risk factor that was significantly correlated with OR and OS in HCC patients. Dramatically impaired PTEN protein expression in HCC patients with family aggregation resulting from hepatitis B and liver cirrhosis was correlated with OR and OS, and impaired PTEN expression was an independent risk factor for prognosis after radical surgery.

[754]

TÍTULO / TITLE: - Low Levels of Interleukin-1 Receptor Antagonist (IL-1RA) Predict Engraftment Syndrome after Autologous Stem Cell Transplantation in POEMS Syndrome and Other Plasma Cell Neoplasms.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biol Blood Marrow Transplant. 2013 Jun 20. pii: S1083-8791(13)00259-0. doi: 10.1016/j.bbmt.2013.06.012.

●● Enlace al texto completo (gratis o de pago)

[1016/j.bbmt.2013.06.012](#)

AUTORES / AUTHORS: - Keyzner A; D'Souza A; Lacy M; Gertz M; Hayman S; Buadi F; Kumar S; Dingli D; Engebretson A; Tong C; Dispenzieri A

INSTITUCIÓN / INSTITUTION: - Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota.

RESUMEN / SUMMARY: - A rare, multisystem, plasma cell neoplasm, POEMS (polyradiculoneuropathy, organomegaly, endocrinopathy, M-spike, skin changes) syndrome is characterized by an abundance of proinflammatory and angiogenic cytokines. Patients with POEMS are known to have a high incidence of engraftment syndrome after autologous stem cell transplantation. We conducted a pilot study assessing levels of 30 different pro- and anti-inflammatory cytokines before and serially after transplantation in 18 patients with plasma cell neoplasms: POEMS syndrome (n = 9), multiple myeloma (n = 4), and amyloidosis (n = 5). We show that POEMS patients have higher pretransplantation levels of IL-4, IL-10, IL-13, IFN-alpha, and EGF as compared with those with non-POEMS plasma cell neoplasms. Higher pre- and posttransplantation IL-13 levels correlated with delayed neutrophil engraftment in POEMS patients. Low posttransplantation IL-1RA levels correlated with

engraftment syndrome in both POEMS and non-POEMS patients. We conclude that differences in the peri-transplantation cytokine milieu may explain the higher transplantation morbidity in patients with POEMS syndrome. Our results need validation in a larger cohort.

[755]

TÍTULO / TITLE: - Secretory clusterin (sCLU) overexpression is associated with resistance to preoperative neoadjuvant chemotherapy in primary breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur Rev Med Pharmacol Sci. 2013 May;17(10):1337-44.

AUTORES / AUTHORS: - Niu ZH; Wang Y; Chun B; Li CX; Wu L

INSTITUCIÓN / INSTITUTION: - The center of Breast disease, the Affiliated Hospital of Qingdao Medical College, Qingdao University, Qingdao, R.P. China.

RESUMEN / SUMMARY: - **OBJECTIVES:** Preoperative chemotherapy is often used in patients with locally advanced breast cancer. However, commonly used clinical and pathological parameters are poor predictors of response to this type of therapy. The secreted form of the CLU protein (sCLU) is a glycosylated protein of 76-80 kDa. It has become increasingly clear that in most cells sCLU is a stress-associated cytoprotective protein that is upregulated by various apoptotic triggers. Furthermore, sCLU confers resistance by some unknown mechanism when overexpressed. The purpose of the present study was to examine the sCLU proteins as predictors of clinical outcome and response to chemotherapy in locally advanced breast cancer. **PATIENTS AND METHODS:** The expression levels of sCLU was determined by immunohistochemistry before preoperative chemotherapy in 72 patients with locally advanced breast cancer. All patients were treated with cyclophosphamide/doxorubicin/5-FU(CAF) and some patients received additional treatment with docetaxel. Expression data were compared with patients' clinical and pathological features, clinical outcome, and response to chemotherapy. **RESULTS:** The results showed sCLU expression before preoperative chemotherapy was inversely related to the tumor size, expression of estrogen and progesterone receptors. High preoperative expression of sCLU was associated with resistance to CAF therapy, but not with resistance to docetaxel. **CONCLUSIONS:** We, therefore, suggested sCLU expression may be a useful marker for predicting response to preoperative chemotherapy and clinical outcome in patients with locally advanced breast cancer.

[756]

TÍTULO / TITLE: - BCL-2 hypermethylation is a potential biomarker of sensitivity to anti-mitotic chemotherapy in endocrine-resistant breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0012](https://doi.org/10.1158/1535-7163.MCT-13-0012)

AUTORES / AUTHORS: - Stone A; Cowley MJ; Valdes-Mora F; McCloy RA; Sergio CM; Gallego-Ortega D; Caldon CE; Ormandy CJ; Biankin AV; Gee JM; Nicholson RI; Print CG; Clark SJ; Musgrove EA

INSTITUCIÓN / INSTITUTION: - 1Cancer Research Program, Garvan Institute of Medical Research.

RESUMEN / SUMMARY: - Overexpression of the anti-apoptotic factor, BCL-2, is a frequent feature of malignant disease and is commonly associated with poor prognosis and resistance to conventional chemotherapy. In breast cancer, however, high BCL-2 expression is associated with favourable prognosis, estrogen receptor (ER) positivity and low tumour grade; whilst low expression is included in several molecular signatures associated with resistance to endocrine therapy. In the present study, we correlate BCL-2 expression and DNA methylation profiles in human breast cancer and in multiple cell models of acquired endocrine-resistance to determine whether BCL-2 hypermethylation could provide a useful biomarker of response to cytotoxic therapy. In human disease, diminished expression of BCL-2 was associated with hypermethylation of the second exon, in a region that overlapped a CpG island and an ER-binding site. Hypermethylation of this region, which occurred in 10% of primary tumours, provided a stronger predictor of patient survival ($p=0.019$) when compared to gene expression ($n=522$). In multiple cell-models of acquired endocrine-resistance, BCL-2 expression was significantly reduced in parallel with increased DNA methylation of the exon 2 region. The reduction of BCL-2 expression in endocrine-resistant cells lowered their apoptotic threshold to anti-mitotic agents: nocodazole, paclitaxel and the PLK1 inhibitor, BI2536. This phenomenon could be reversed with ectopic expression of BCL-2, and rescued with the BCL-2 inhibitor, ABT-737. Collectively, these data imply that BCL-2 hypermethylation provides a robust biomarker of response to current and next generation cytotoxic agents in endocrine-resistant breast cancer, which may prove beneficial in directing therapeutic strategy for patients with non-resectable, metastatic disease.

[757]

TÍTULO / TITLE: - Cytosolic phosphorylated EGFR is predictive of recurrence in early stage penile cancer patients: a retrospective study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Transl Med. 2013 Jul 2;11(1):161.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-161](https://doi.org/10.1186/1479-5876-11-161)

AUTORES / AUTHORS: - Di Lorenzo G; Perdon S; Buonerba C; Sonpavde G; Gigantino V; Pannone G; Quarto G; Ferro M; Gaudio G; Terracciano D; Di Trollo R; Rescigno P; Botti G; De Placido S; Facchini G; Ascierto PA; Franco R

RESUMEN / SUMMARY: - BACKGROUND: Penile cancer (PC) is a rare tumor, and therapeutic options are limited for this disease, with an overall 5-year overall survival around 65-70%. Adjuvant therapy is not recommended for patients with N0-1 disease, despite up to 60% of these patients will die within 5 years from diagnosis. METHODS: Medical records of all patients who underwent radical surgery at University Federico II of Naples and at National Tumor Institute "Pascale" of Naples for early squamous cell carcinoma of the penis from January, 2000 to December, 2011 were retrieved. Paraffin wax embedded tissue specimens were retrieved from the pathology archives of the participating Institutions for all patients. Expression of p-EGFR, EGFR and positivity to HPV were evaluated along with other histological variables of interest. Demographic data of eligible patients were retrieved along with clinical characteristics such as type of surgical operation, time of follow up, time of recurrence, overall survival. A multivariable model was constructed using a forward stepwise selection procedure. RESULTS: Thirty eligible patients were identified. All patients were positive for EGFR by immunohistochemistry, while 13 and 16 were respectively positive for nuclear and cytosolic p-EGFR. No EGFR amplification was detected by FISH. Eight patients were positive for high-risk HPV by ISH. On univariable analysis, corpora cavernosa infiltration (OR 7.8; 95% CI = 0,8 to 75,6; P = 0,039) and positivity for cytosolic p-EGFR (OR 7.6; 95% CI = 1.49 to 50; P = 0.009) were predictive for recurrence, while only positivity for cytosolic p-EGFR (HR =9.0; 95% CI 1.0-100; P = 0,0116) was prognostic for poor survival. CONCLUSION: It is of primary importance to identify patients with N0-1 disease who are at increased risk of recurrence, as they do not normally receive any adjuvant therapy. Expression of p-EGFR was found in this series to be strongly related to increase risk of recurrence and shorter overall survival. This finding is consistent with the role of p-EGFR in other solid malignancies. Integration of p-EGFR with classic prognostic factors and other histology markers should be pursued to establish optimal adjuvant therapy for N0-1 PC patients.

[758]

TÍTULO / TITLE: - Targeted Delivery of Dendritic Polyglycerol-Doxorubicin Conjugates by scFv-SNAP Fusion Protein Suppresses EGFR Cancer Cell Growth.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomacromolecules. 2013 Jul 3.

●● Enlace al texto completo (gratis o de pago) [1021/bm400410e](#)

AUTORES / AUTHORS: - Hussain AF; Kruger HR; Kampmeier F; Weissbach T; Licha K; Kratz F; Haag R; Calderon M; Barth S

INSTITUCIÓN / INSTITUTION: - Department of Gynecology and Obstetrics, University Hospital RWTH Aachen , Pauwelsstrasse 30, 52074, Aachen, Germany.

RESUMEN / SUMMARY: - Development of effective polymer-based nanocarriers for the successful application in cancer therapy still remains a great challenge in current research. In the present study we present a dendritic polyglycerol-based multifunctional drug immunoconjugate that specifically targets and kills cancer cell lines expressing epidermal growth factor receptor (EGFR). The nanocarrier was provided with a dendritic core as a multifunctional anchoring point, doxorubicin (Doxo) coupled through a pH-sensitive linker, a fluorescence marker, poly(ethylene glycol), as solubilizing and shielding moiety, and a scFv antibody conjugated through the SNAP-Tag technology. The study provides the proof of principle that SNAP-tag technology can be used to generate drug-carrying nanoparticles efficiently modified with single-chain antibodies to specifically target and destroy cancer cells.

[759]

TÍTULO / TITLE: - Neoadjuvant Doxorubicin/Cyclophosphamide Followed by Ixabepilone or Paclitaxel in Early Stage Breast Cancer and Evaluation of betaIII-Tubulin Expression as a Predictive Marker.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncologist. 2013;18(7):787-94. doi: 10.1634/theoncologist.2013-0075. Epub 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago)

[1634/theoncologist.2013-0075](#)

AUTORES / AUTHORS: - Saura C; Tseng LM; Chan S; Chacko RT; Campone M; Manikhas A; Nag SM; Leichman CG; Dasappa L; Fasching PA; Hurtado de Mendoza F; Symmans WF; Liu D; Mukhopadhyay P; Horak C; Xing G; Pusztai L

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, España;

RESUMEN / SUMMARY: - This randomized phase II trial was designed to compare the rate of pathologic complete response (pCR) induced by neoadjuvant cyclophosphamide plus doxorubicin (AC) followed by ixabepilone or paclitaxel in women with early stage breast cancer (BC). Expression of betaIII-tubulin as a predictive marker was also evaluated. Patients and Methods. Women with untreated, histologically confirmed primary invasive breast adenocarcinoma received four cycles of AC followed by 1:1 randomization to either ixabepilone 40 mg/m² (3-hour infusion) every 3 weeks for four cycles (n = 148) or weekly paclitaxel 80 mg/m² (1-hour infusion) for 12 weeks (n = 147). All patients underwent a core needle biopsy of the primary cancer for molecular marker analysis prior to chemotherapy. betaIII-Tubulin expression was assessed using immunohistochemistry. Results. There was no significant difference in the rate of pCR in the ixabepilone treatment arm (24.3%; 90% confidence interval [CI], 18.6-30.8) and the paclitaxel treatment arm (25.2%; 90% CI, 19.4-31.7). betaIII-Tubulin-positive patients obtained higher pCR rates compared with betaIII-

tubulin-negative patients in both treatment arms; however, betaIII-tubulin expression was not significantly associated with a differential response to ixabepilone or paclitaxel. The safety profiles of both regimens were generally similar, although neutropenia occurred more frequently in the ixabepilone arm (grade \geq 4: 41.3% vs. 8.4%). The most common nonhematologic toxicity was peripheral neuropathy. Conclusions. Neoadjuvant treatment of early stage BC with AC followed by ixabepilone every 3 weeks or weekly paclitaxel was well tolerated with no significant difference in efficacy. Higher response rates were observed among betaIII-tubulin-positive patients.

[760]

TÍTULO / TITLE: - Co-polysomy of chromosome 1q and 19p predicts worse prognosis in 1p/19q codeleted oligodendroglial tumors: FISH analysis of 148 consecutive cases.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neuro Oncol. 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not092](#)

AUTORES / AUTHORS: - Ren X; Jiang H; Cui X; Cui Y; Ma J; Jiang Z; Sui D; Lin S

INSTITUCIÓN / INSTITUTION: - Neurosurgery (X.R., H.J., Y.C., J.M., Z.J., D.S., S.L.) and Pharmacology (X.C.), Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

RESUMEN / SUMMARY: - Background This study aimed to evaluate the prognostic significance of co-polysomy of chromosome 1q and 19p in 1p/19q codeleted oligodendroglial tumors (ODGs). Methods In a series of 148 ODGs with 1p/19q deletion, co-polysomy of 1q and 19p was detected by fluorescence in situ hybridization (FISH). Log-rank analysis and Cox regression methods were used to compare Kaplan-Meier plots and identify factors associated with worse prognosis. Results There were 104 (70.3%) low-grade ODGs and 44 (29.7%) high-grade ODGs. Co-polysomy was independently associated with shorter progression-free survival and overall survival in 1p/19q codeleted ODGs, irrespective of tumor grades. The odds ratio of without and with co-polysomy was 0.263 (95% confidence interval [CI], 0.089-0.771; P = .015) for progression-free survival and 0.213 (95% CI, 0.060-0.756; P = .017) for overall survival. Subgroup analysis confirmed this trend in both low-grade and high-grade ODGs, although the P value for high-grade ODGs was marginally significant. Conclusions Co-polysomy of 1q and 19p could be used as a marker to independently predict worse prognoses and guide individual therapy in 1p/19q codeleted ODGs.

[761]

TÍTULO / TITLE: - Osteopontin expressions correlate with WHO grades and predict recurrence in meningiomas.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Brain Tumor Pathol. 2013 Jun 21.

●● Enlace al texto completo (gratis o de pago) [1007/s10014-013-0152-](#)

[2](#)

AUTORES / AUTHORS: - Arikok AT; Onder E; Seckin H; Kacar A; Fesli R; Oguz AS; Alper M

INSTITUCIÓN / INSTITUTION: - Department of Pathology, S.B Ankara Diskapi Research and Training Hospital, Ankara, Turkey, atalina2005@yahoo.com.

RESUMEN / SUMMARY: - Recurrence of meningiomas is a major prognostic issue. Although World Health Organization (WHO) histopathological grading correlates strongly with recurrence, it has some limitations, and predicting the biological behavior of grade I meningiomas is particularly difficult. Osteopontin (OPN) is a protein known to be involved in tumor progression. The purpose of this study is to determine expression of OPN in meningiomas and to investigate its correlation with WHO grades and tumor recurrence. Immunohistochemical (IHC) evaluation of expression of OPN was performed by two different methods to ensure reliability. OPN IHC and Allred scores were calculated on the basis of intensity and extent of staining. Both scores were in agreement and correlated significantly with meningioma grade and Ki-67 index. OPN scores were also significantly correlated with recurrence of WHO grade I meningiomas. Cut-off values for OPN IHC and OPN Allred scores between non-recurrent and recurrent grade I meningiomas were calculated as 70 and 5.5 respectively. We concluded that OPN is a valuable marker for grading meningiomas and for predicting the recurrence in WHO grade I tumors.

[762]

TÍTULO / TITLE: - Considerations for the prediction of survival time in pancreatic cancer based on registry data.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Pharmacokinet Pharmacodyn. 2013 Aug;40(4):527-36. doi: 10.1007/s10928-013-9327-z. Epub 2013 Jul 12.

●● Enlace al texto completo (gratis o de pago) [1007/s10928-013-9327-](#)

[Z](#)

AUTORES / AUTHORS: - Bajaj G; Dombrowsky E; Yu Q; Agarwal B; Barrett JS

INSTITUCIÓN / INSTITUTION: - Laboratory of Applied PK/PD, Department of Clinical Pharmacology and Therapeutics, The Children's Hospital of Philadelphia, Colket Translational Research Building, Room 4012, 3501 Civic Center Blvd, Philadelphia, PA, 19104, USA.

RESUMEN / SUMMARY: - Semi-parametric and parametric survival models in patients with pancreatic adenocarcinoma (PC) using data from Surveillance, Epidemiology, and End Result (SEER) registry were developed to identify

relevant covariates affecting survival, verify against external patient data and predict disease outcome. Data from 82,251 patients was extracted using site and histology codes for PC in the SEER database and refined based on specific cause of death. Predictors affecting survival were selected from SEER database; the analysis dataset included 2,437 patients. Survival models were developed using both semi-parametric and parametric approaches, evaluated using Cox-Snell and deviance residuals, and predictions were assessed using an external dataset from Saint Louis University (SLU). Prediction error curves (PECs) were used to evaluate prediction performance of these models compared to Kaplan-Meier response. Median overall survival time of patients from SEER data was 5 months. Our analysis shows that the PC data from SEER was best fitted by both semi-parametric and the parametric model with log-logistic distribution. Predictors that influence survival included disease stage, grade, histology, tumor size, radiation, chemotherapy, surgery, and lymph node status. Survival time predictions from the SLU dataset were comparable and PECs show that both semi-parametric and parametric models exhibit similar predictive performance. PC survival models constructed from registry data can provide a means to classify patients into risk-based subgroups, to predict disease outcome and aid in the design of future prospective randomized trials. These models can evolve to incorporate predictive biomarker and pharmacogenetic correlates once adequate causal data is established.

[763]

TÍTULO / TITLE: - Association of common gene variants in the WNT/beta-catenin pathway with colon cancer recurrence.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics J. 2013 Jul 2. doi: 10.1038/tpj.2013.20.

●● Enlace al texto completo (gratis o de pago) [1038/tpj.2013.20](#)

AUTORES / AUTHORS: - Paez D; Gerger A; Zhang W; Yang D; Labonte MJ; Benhaim L; Kahn M; Lenz F; Lenz C; Ning Y; Wakatsuki T; Loupakis F; Lenz HJ

INSTITUCIÓN / INSTITUTION: - [1] Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA [2] Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, España.

RESUMEN / SUMMARY: - Wnt/beta-catenin signaling has a central role in the development and progression of most colon cancers (CCs). Germline variants in Wnt/beta-catenin pathway genes may result in altered gene function and/or activity, thereby causing inter-individual differences in relation to tumor recurrence capacity and chemoresistance. We investigated germline polymorphisms in a comprehensive panel of Wnt/beta-catenin pathway genes to predict time to tumor recurrence (TTR) in patients with stage III and high-risk

stage II CC. A total of 234 patients treated with 5-fluorouracil-based chemotherapy were included in this study. Whole-blood samples were analyzed for putative functional germline polymorphisms in SFRP3, SFRP4, DKK2, DKK3, Axin2, APC, TCF7L2, WNT5B, CXXC4, NOTCH2 and GLI1 genes by PCR-based restriction fragment-length polymorphism or direct DNA sequencing. Polymorphisms with statistical significance were validated in an independent study cohort. The minor allele of WNT5B rs2010851 T>G was significantly associated with a shorter TTR (10.7 vs 4.9 years; hazard ratio: 2.48; 95% CI, 0.96-6.38; P=0.04) in high-risk stage II CC patients. This result remained significant in multivariate Cox's regression analysis. This study shows that the WNT5B germline variant rs2010851 was significantly identified as a stage-dependent prognostic marker for CC patients after 5-fluorouracil-based adjuvant therapy. The Pharmacogenomics Journal advance online publication, 2 July 2013; doi:10.1038/tpj.2013.20.

[764]

TÍTULO / TITLE: - Phase I-II Clinical Trial of Oxaliplatin, Fludarabine, Cytarabine, and Rituximab Therapy in Aggressive Relapsed/Refractory Chronic Lymphocytic Leukemia or Richter Syndrome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Jun 26. pii: S2152-2650(13)00112-2. doi: 10.1016/j.clml.2013.03.012.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.03.012

AUTORES / AUTHORS: - Tsimberidou AM; Wierda WG; Wen S; Plunkett W; O'Brien S; Kipps TJ; Jones JA; Badoux X; Kantarjian H; Keating MJ

INSTITUCIÓN / INSTITUTION: - Department of Investigational Cancer Therapeutics, Phase I Clinical Trials Program, The University of Texas MD Anderson Cancer Center, Houston, TX. Electronic address: atsimber@mdanderson.org.

RESUMEN / SUMMARY: - BACKGROUND: To improve outcomes of patients with Richter syndrome (RS) and relapsed/refractory chronic lymphocytic leukemia (CLL), we modified the OFAR1 regimen (oxaliplatin and cytarabine doses of the oxaliplatin, fludarabine, cytarabine, and rituximab) for this phase I-II study (OFAR2). PATIENTS AND METHODS: OFAR2 consisted of oxaliplatin at 30 mg/m² on days 1 to 4, fludarabine at 30 mg/m², cytarabine at 0.5 g/m², rituximab at 375 mg/m² on day 3, and pegfilgrastim at 6 mg on day 6. Fludarabine and cytarabine were given on days 2 and 3 (cohort 1), days 2 to 4 (cohort 2), or days 2 to 5 (cohort 3) every 4 weeks. Phase II followed the "3 + 3" design of phase I. RESULTS: The 102 patients (CLL, 67; RS, 35) treated had heavily pretreated high-risk disease. Twelve patients were treated in phase I; cohort 2 was the phase II recommended dose. The most common toxicities were hematologic. Response rates (phase II) were 38.7% for RS (complete response [CR], 6.5%) and 50.8% for relapsed/refractory CLL (CR, 4.6%). The

median survival durations were 6.6 (RS) and 20.6 (CLL) months. Among 9 patients who underwent allogeneic stem cell transplantation (SCT) as post-remission therapy, none has died (median follow-up, 15.9 months).

CONCLUSION: OFAR2 had significant antileukemic activity in RS and relapsed/refractory CLL. Patients undergoing SCT as post-remission therapy had favorable outcomes.

[765]

- CASTELLANO -

TÍTULO / TITLE: Bestrahlung der kraniospinalen Achse mit simultaner Gabe von Temozolomid und Nimotuzumab bei einem Kind mit primär metastasiertem diffus intrinsischem Ponsgliom : Ein individueller Heilversuch.

TÍTULO / TITLE: - Craniospinal irradiation with concurrent temozolomide and nimotuzumab in a child with primary metastatic diffuse intrinsic pontine glioma : A compassionate use treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Strahlenther Onkol. 2013 Aug;189(8):693-696. Epub 2013 Jun 12.

●● Enlace al texto completo (gratis o de pago) [1007/s00066-013-0370-](http://1007/s00066-013-0370-x)

[X](#)

AUTORES / AUTHORS: - Muller K; Schlamann A; Seidel C; Warmuth-Metz M; Christiansen H; Vordermark D; Kortmann RD; Kramm CM; von Bueren AO

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University Medical Center Leipzig, Stephan-Str. 9^a, 04103, Leipzig, Germany, Klaus.Mueller@medizin.uni-leipzig.de.

RESUMEN / SUMMARY: - Primary metastatic diffuse intrinsic pontine glioma (DIPG) is relatively rare and associated with a dismal prognosis. Combining craniospinal irradiation (CSI) with concurrent temozolomide and nimotuzumab therapy may slightly improve tumor control and overall survival. However, little is known about the feasibility and toxicity of this treatment approach. Here, we describe the case of an 8-year-old girl with primary metastatic DIPG who received craniospinal radiotherapy, a local boost, and concurrent temozolomide and nimotuzumab treatment based on an individual therapy recommendation. Radiotherapy could be completed without any interruption. However, concurrent temozolomide had to be disrupted several times due to considerable acute myelotoxicity (grade III-IV). Maintenance immunochemotherapy could be started with a delay of 5 days and was performed according to treatment schedule. The disease could be stabilized for a few months. A routine MRI scan finally depicted disease progression 5.7 months after the start of irradiation. The patient died 1.9 months later.

[766]

TÍTULO / TITLE: - A ZMYM2-FGFR1 8p11 myeloproliferative neoplasm with a novel nonsense RUNX1 mutation and tumor lysis upon imatinib treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Genet. 2013 Apr;206(4):140-4. doi: 10.1016/j.cancergen.2013.04.001.

- Enlace al texto completo (gratis o de pago)

1016/j.cancergen.2013.04.001

AUTORES / AUTHORS: - Buijs A; van Wijnen M; van den Blink D; van Gijn M; Klein SK

INSTITUCIÓN / INSTITUTION: - Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands. a.buijs@umcutrecht.nl

RESUMEN / SUMMARY: - The 8p11 myeloproliferative neoplasm (8p11 MPN) is a rare disorder that is molecularly characterized by fusions of diverse partners to the tyrosine kinase receptor gene FGFR1. It can rapidly transform to acute myeloid leukemia. Here we report on a case with a t(8;13)(p11.2;q12.1) ZMYM2-FGFR1 fusion, with massive tumor lysis upon tyrosine kinase inhibition with imatinib. Upon reevaluation, we detected trisomy 21 in addition to the translocation. Sequencing revealed a nonsense c.958C -->T RUNX1 mutation both at diagnosis and disease progression, resulting in a p.Arg320X carboxyl-terminal truncated RUNX1 protein. This is the first report on an 8p11 MPN with a trisomy 21 RUNX1 mutation.

[767]

TÍTULO / TITLE: - FOXA1 expression after neoadjuvant chemotherapy is a prognostic marker in estrogen receptor-positive breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Breast Cancer. 2013 Jun 16.

- Enlace al texto completo (gratis o de pago) [1007/s12282-013-0482-](http://1007/s12282-013-0482-2)

[2](#)

AUTORES / AUTHORS: - Kawase M; Toyama T; Takahashi S; Sato S; Yoshimoto N; Endo Y; Asano T; Kobayashi S; Fujii Y; Yamashita H

INSTITUCIÓN / INSTITUTION: - Oncology, Immunology and Surgery, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, 467-8601, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Recent studies have indicated that the response to chemotherapy and the prognostic impact of a pathological complete response (pCR) after neoadjuvant chemotherapy differ among breast cancer subtypes. Predictors of response to chemotherapy and prognostic factors for survival might be different in estrogen receptor (ER)-positive breast cancer. METHODS: Women with Stage II to III ER-positive HER2-negative breast cancer treated with anthracycline and taxane-containing neoadjuvant chemotherapy between 2003 and 2011 were retrospectively analyzed. Expression of forkhead box A1 (FOXA1), B cell lymphoma 2 (BCL2) and microtubule-associated protein tau (MAPT) as well as ER, progesterone

receptor, HER2 and Ki67 was examined by immunohistochemistry in pre- and post-treatment specimens. Factors predictive of response to neoadjuvant chemotherapy and distant disease-free survival were analyzed. RESULTS: Tumor grade was positively correlated with Ki67 expression. Expression levels of ER were positively correlated with expression levels of HER2, BCL2, FOXA1 and MAPT in pre-treatment tumors. The Ki67 labeling index was the only factor that was significantly associated with clinical response measured by the reduction of tumor volume and pCR. Lymph node status, expression of ER before neoadjuvant chemotherapy and expression of FOXA1 after neoadjuvant chemotherapy were significantly associated with distant disease-free survival, both by univariate and multivariate analyses. CONCLUSIONS: Patients with ER-positive HER2-negative breast cancer should be selected for neoadjuvant chemotherapy. FOXA1 expression could be a prognostic marker in ER-positive breast cancer.

[768]

TÍTULO / TITLE: - Dual kinin B1 and B2 receptor activation provides enhanced blood-brain barrier permeability and anticancer drug delivery into brain tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 14;14(9).

AUTORES / AUTHORS: - Cote J; Savard M; Neugebauer W; Fortin D; Lepage M; Gobeil F

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology; Faculty of Medicine and Health Sciences; Universite de Sherbrooke; Sherbrooke, Canada; Department of Nuclear Medicine and Radiobiology; Faculty of Medicine and Health Sciences; Universite de Sherbrooke; Sherbrooke, Canada; Institute of Pharmacology (IPS); Faculty of Medicine and Health Sciences; Universite de Sherbrooke; Sherbrooke, Canada.

RESUMEN / SUMMARY: - The low permeability of the BBB is largely responsible for the lack of effective systemic chemotherapy against primary and metastatic brain tumors. Kinin B1R and B2R have been shown to mediate reversible tumor-selective BBB disruption in preclinical animal models. We investigated whether co-administration of two novel potent kinin B1R and B2R agonists offers an advantage over administering each agonist alone for enhancing BBB permeability and tumor targeting of drugs in the malignant F98 glioma rat model. A new covalent kinin heterodimer that equally stimulates B1R and B2R was also constructed for the purpose of our study. We found that co-administration of B1R and B2R agonists, or alternatively administration of the kinin heterodimer more effectively delivered the MRI contrast agent Gd-DTPA and the anticancer drug carboplatin to brain tumors and surrounding tissues than the agonists alone (determined by MRI and ICP-MS methods). Importantly, the efficient delivery of carboplatin by the dual kinin receptor targeting on the BBB translated into increased survival of glioma-bearing rats. Thus, this report

describes a potential strategy for maximizing the brain bioavailability and therapeutic efficacy of chemotherapeutic drugs.

[769]

TÍTULO / TITLE: - Uracil DNA glycosylase expression determines human lung cancer cell sensitivity to pemetrexed.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jul 19.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0172](#)

AUTORES / AUTHORS: - Weeks LD; Fu P; Gerson SL

INSTITUCIÓN / INSTITUTION: - 1Pathology, Case Western Reserve University.

RESUMEN / SUMMARY: - Uracil misincorporation into DNA is a consequence of pemetrexed inhibition of thymidylate synthetase. The base excision repair (BER) enzyme, uracil DNA glycosylase (UNG) is the major glycosylase responsible for removal of misincorporated uracil. We previously illustrated hypersensitivity to pemetrexed in UNG-/- human colon cancer cells. Here, we examined the relationship between UNG expression and pemetrexed sensitivity in human lung cancer. We observed a spectrum of UNG expression in human lung cancer cells. Higher levels of UNG are associated with pemetrexed resistance and are present in cell lines derived from pemetrexed-resistant histological subtypes (small cell and squamous cell carcinoma). Acute pemetrexed exposure induces UNG protein and mRNA, consistent with up-regulation of uracil-DNA repair machinery. Chronic exposure of H1299 adenocarcinoma cells to increasing pemetrexed concentrations established drug-resistant sublines. Significant induction of UNG protein confirmed up-regulation of BER as a feature of acquired pemetrexed resistance. Co-treatment with the BER inhibitor, methoxyamine (MX) overrides pemetrexed resistance in chronically exposed cells, underscoring the utility of BER directed therapeutics to offset acquired drug resistance. Expression of UNG-directed siRNA and shRNA enhanced sensitivity in A549 and H1975 cells, and in drug-resistant sublines, confirming that UNG up-regulation is protective. In human lung cancer, UNG deficiency is associated with pemetrexed-induced retention of uracil in DNA that destabilizes DNA replication forks resulting in DNA double strand breaks and cell death. Thus, in experimental models, UNG is a critical mediator of pemetrexed sensitivity that warrants evaluation to determine clinical value.

[770]

TÍTULO / TITLE: - Validity of aspartate aminotransferase to platelet ratio index as predictor of early viral response in patients with hepatitis C treated by interferon-based therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Pak Med Assoc. 2012 Oct;62(10):1008-11.

AUTORES / AUTHORS: - Samiullah S; Bikharam D; Musarat K

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Liaquat University of Medical & Health Sciences, Jamshoro, Hyderabad.

shaikhsamiullah@yahoo.com

RESUMEN / SUMMARY: - **OBJECTIVE:** To observe any change in value of aspartate aminotransferase to platelet ratio index from the baseline and to compare it with the Hepatitis C virus ribonucleic acid at 12 weeks after the start of interferon-based treatment in patients with Hepatitis C. **METHODS:** The prospective study, conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital, Jamshoro, Pakistan, from September 2009 to March 2010, included 158 consecutive, chronic patients of Hepatitis C with grade ≥ 2 fibrosis on liver biopsy, or having aspartate aminotransferase/Platelet ratio index of > 1 . The aspartate aminotransferase to platelet ratio index was determined as aspartate aminotransferase level (upper normal limit)/platelets counts (10⁹/L) \times 100. Eligible patients were assigned to receive thrice weekly subcutaneous injection of 3MIU standard interferon ≥ 2 and weight-base dosage of ribavirin. The early virological response was defined as undetectable Hepatitis C virus ribonucleic acid test at week 12 of the study. APRI < 1 was considered to be the response to therapy. Paired sample t-test was applied to observe pre-and post-treatment mean \pm SD of continuous variables, while Chi-square test was applied for comparing categorical variables. A p-value of 0.05 was considered statistically significant. **RESULTS:** Out of 158 patients enrolled, 90 fulfilled the inclusion criteria. The aspartate aminotransferase to platelet ratio index before treatment was 1.61 \pm 1.00 and after treatment 1.10 \pm 1.08. Hepatitis C virus ribonucleic acid after 12 weeks of treatment was non-detectable (early viral response achieved) in 72 (80%) patients. A strong relation was found between aspartate aminotransferase to platelet ratio index and Negative polymerase chain reaction with early virological response as only 2 (4.5%) patients with negative polymerase chain reaction at 12 weeks had aspartate aminotransferase to platelet ratio index > 1 ($p = 0.001$). **CONCLUSIONS:** APRI can act as a predictor of early viral response in patients with Hepatitis C.

[771]

TÍTULO / TITLE: - Focal adhesion kinase autophosphorylation inhibition decreases colon cancer cell growth and enhances the efficacy of chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 3;14(8).

AUTORES / AUTHORS: - Heffler M; Golubovskaya VM; Dunn KM; Cance W

INSTITUCIÓN / INSTITUTION: - Department of Surgical Oncology; Roswell Park Cancer Institute and the University at Buffalo/State University of New York; Buffalo, NY USA.

RESUMEN / SUMMARY: - Focal adhesion kinase (FAK) increasingly has been implicated in cancer growth and progression. 1,2,4,5-Benzenetetraamine tetrahydrochloride (Y15) is a small molecule FAK inhibitor that blocks the Y397 autophosphorylation site. FAK inhibitor, Y15 decreased Y397 FAK in different colon cancer cells lines in a dose-dependent manner. In addition, Y15 decreased phosphorylated Src in SW480 and SW620 cells. Y15 decreased cell viability, increased detachment and increased apoptosis in SW480 and SW620 cells in vitro. Combination of FAK inhibitor Y15 and Src inhibitor PP2 decreased colon cancer cell viability more effectively than each agent alone. In addition, when combined with 5-FU, oxaliplatin or 5-FU and oxaliplatin, colon cancer viability was decreased further, demonstrating that dual and triple therapy synergistically inhibits cell viability. In vivo, Y15 decreased subcutaneous SW620 tumor growth by 28%. Combination of oral Y15 with 5-FU/or oxaliplatin decreased tumor growth by 48% more effectively than each inhibitor alone. Finally, tumors treated with Y15 expressed less Y397 phosphorylation, Src phosphorylation and had greater apoptosis than controls. Thus, the small molecule FAK inhibitor, Y15, inhibits cell growth in vitro and in vivo and enhances the efficacy of chemotherapy, demonstrating that it can be an effective therapeutic inhibitor for treating colon cancer.

[772]

TÍTULO / TITLE: - Positron Emission Tomography Imaging of Drug-Induced Tumor Apoptosis with a Caspase-Triggered Nanoaggregation Probe.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Angew Chem Int Ed Engl. 2013 Jul 23. doi: 10.1002/anie.201303422.

●● Enlace al texto completo (gratis o de pago) [1002/anie.201303422](#)

AUTORES / AUTHORS: - Shen B; Jeon J; Palner M; Ye D; Shuhendler A; Chin FT; Rao J

INSTITUCIÓN / INSTITUTION: - Department of Radiology, Molecular Imaging Program at Stanford, Stanford University School of Medicine, Stanford, CA 94305-5484 (USA).

RESUMEN / SUMMARY: - Drug Design: An 18 F-labeled caspase-3-sensitive nanoaggregation positron emission tomography tracer was prepared and evaluated for imaging the caspase-3 activity in doxorubicin-treated tumor xenografts. Enhanced retention of the 18 F activity in apoptotic tumors is achieved through intramolecular macrocyclization and in situ aggregation upon caspase-3 activation.

[773]

TÍTULO / TITLE: - Pharmacogenetics, Pharmacogenomics and Epigenetics of Nrf2-regulated Xenobiotic-metabolizing Enzymes and Transporters by Dietary Phytochemical and Cancer Chemoprevention.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Curr Drug Metab. 2013 Jul 1;14(6):688-94.

AUTORES / AUTHORS: - Wu TY; Khor TO; Lee JH; Cheung KL; Shu L; Chen C; Kong AN

INSTITUCIÓN / INSTITUTION: - Ernest Mario School of Pharmacy, Room 228, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, USA. kongt@pharmacy.rutgers.edu.

RESUMEN / SUMMARY: - Cancer chemopreventive activities of various phytochemicals have been attributed to the modulation of xenobiotic disposition, which includes absorption, distribution, metabolism, and excretion. The interaction between xenobiotics and xenobiotic-metabolizing enzymes (XMEs) is bidirectional. XMEs are responsible for the biotransformation of xenobiotics such as bioactivation and detoxification. Conversely, xenobiotics affect XMEs through transcriptional regulation (induction or suppression) and post-translational interactions (inhibition or activation). Similar relationships also exist between xenobiotics and their transporters. Studies conducted over the past decade have demonstrated that the transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), plays a critical role in the regulation of detoxifying enzymes and transporters through a signaling system that senses and responds to redox imbalance. The role of Nrf2 in the interaction between chemopreventive phytochemicals and detoxifying enzymes/transporters has become an important topic in cancer chemoprevention. In this review, the genetic and epigenetic factors that contribute to Nrf2-mediated regulation of detoxifying XMEs and transporters are discussed in the context of cancer chemoprevention. Phytochemicals may modulate the genome as well as epigenome, altering the regulation of XMEs and transporters, which may be critical for both cancer chemoprevention and the prevention of other oxidative stress- and inflammatory-related diseases, including cardiovascular, metabolic and neurological pathologies. The pharmacogenomic expression of XMEs and transporters, with an emphasis on both genomics and epigenetics, will also be discussed.

[774]

TÍTULO / TITLE: - Synthesis and biological evaluation of ursolic acid-triazolyl derivatives as potential anti-cancer agents.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Med Chem. 2013 Aug;66:238-45. doi: 10.1016/j.ejmech.2013.05.029. Epub 2013 Jun 7.

- Enlace al texto completo (gratis o de pago)

[1016/j.ejmech.2013.05.029](https://doi.org/10.1016/j.ejmech.2013.05.029)

AUTORES / AUTHORS: - Rashid S; Dar BA; Majeed R; Hamid A; Bhat BA

INSTITUCIÓN / INSTITUTION: - Medicinal Chemistry Division, Indian Institute of Integrative Medicine, Sanatnagar-Srinagar 190005, Jammu & Kashmir, India.

RESUMEN / SUMMARY: - A series of ursolic acid-1-phenyl-1H-[1,2,3]triazol-4-ylmethylester congeners have been designed and synthesized in an attempt to develop potent antitumor agents. A regioselective approach using Huisgen 1,3-dipolar cycloaddition reaction of ursolic acid-alkyne derivative with various aromatic azides was employed to target an array of triazolyl derivatives in an efficient manner. Their structures were confirmed by using (1)H NMR, (13)C NMR, IR and MS analysis. All the compounds were evaluated for anti-cancer activity against a panel of four human cancer cell lines including A-549 (lung), MCF-7 (breast), HCT-116 (colon), THP-1 (leukemia) and a normal human epithelial cell line (FR-2) using sulforhodamine-B assay. The pharmacological results showed that most of the compounds displayed high level of antitumor activities against the tested cancer cell lines compared with ursolic acid. Compounds 7b, 7g, 7p and 7r were found to be the most potent compounds in this study.

[775]

TÍTULO / TITLE: - Potential epigenetic biomarkers for the diagnosis and prognosis of pancreatic ductal adenocarcinomas.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Rev Mol Diagn. 2013 Jun;13(5):431-43. doi: 10.1586/erm.13.38.

- Enlace al texto completo (gratis o de pago) [1586/erm.13.38](https://doi.org/10.1586/erm.13.38)

AUTORES / AUTHORS: - Hinton J; Callan R; Bodine C; Glasgow W; Brower S; Jiang SW; Li J

INSTITUCIÓN / INSTITUTION: - School of Medicine, Mercer University, Savannah, GA 31404, USA.

RESUMEN / SUMMARY: - With an estimated 37,000 deaths per year, pancreatic cancer is the fourth leading cause of cancer deaths in the USA. A total of 95% of pancreatic cancers are exocrine neoplasms, known as pancreatic ductal adenocarcinomas (PDACs). The difficulty of early diagnosis and the high prevalence of metastasis associated with PDAC contribute to its dismal prognosis. The past decade has witnessed intensive study and impressive progress in searching for more sensitive, specific and cost-effective biomarkers. This review focuses on the epigenetic biomarkers potentially useful for the management of PDAC. The authors begin with an overview on the available biomarkers, and subsequently discuss the recent development in epigenetic biomarkers, including DNA methylation, miRNA and histone modifications in diversified specimens of cell lines, xenograft, cancer tissues, pancreatic juice

and patient blood. These findings raise the possibility for clinical application of epigenetic biomarkers towards screening, early diagnosis, prognosis, chemosensitivity prediction and recurrence surveillance of PDAC patients.

[776]

TÍTULO / TITLE: - Down-regulation of microRNA-181b is a potential prognostic marker of non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pathol Res Pract. 2013 Jun 6. pii: S0344-0338(13)00131-3. doi: 10.1016/j.prp.2013.04.018.

●● [Enlace al texto completo \(gratis o de pago\) 1016/j.prp.2013.04.018](#)

AUTORES / AUTHORS: - Yang J; Liu H; Wang H; Sun Y

INSTITUCIÓN / INSTITUTION: - Department of Radiotherapy and Chemotherapy, People's Hospital of Tangshan City, Hebei Province, PR China. Electronic address: yangjq_ts@163.com.

RESUMEN / SUMMARY: - The aim of this study was to investigate the clinical significance of microRNA-181b (miR-181b) expression in non-small cell lung cancer (NSCLC). MiR-181b expression in 126 pairs of surgically removed NSCLC tissues and their corresponding normal lung tissues was measured by real-time quantitative RT-PCR assay. Additionally, the correlation of miR-181b expression with clinicopathological factors or prognosis of patients was analyzed. At first, miR-181b expression was significantly down-regulated in NSCLC tissues as compared with their normal counterparts ($P < 0.001$). Then, the low miR-181b expression was found to be closely correlated with larger tumor size ($P = 0.02$), higher p-TNM stage ($P = 0.008$) and positive lymph node metastasis ($P = 0.03$) of NSCLC patients. After that, survival analysis found that the overall survival ($P = 0.001$) and disease-free survival ($P = 0.008$) of NSCLC patients with low miR-181b expression were both significantly poorer compared to those patients with high miR-181b expression. Finally, both univariate and multivariate analyses demonstrated that low miR-181b expression may be a poor prognostic marker of NSCLC patients. This is the first study to indicate that down-regulation of miR-181b may be correlated with aggressive disease progression and poor prognosis of NSCLC patients, suggesting that miR-181b might be involved in lung carcinogenesis and become a potential prognostic marker for NSCLC.

[777]

TÍTULO / TITLE: - Astaxanthin inhibits NF-kappaB and Wnt/beta-catenin signaling pathways via inactivation of Erk/MAPK and PI3K/Akt to induce intrinsic apoptosis in a hamster model of oral cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biochim Biophys Acta. 2013 Oct;1830(10):4433-44. doi: 10.1016/j.bbagen.2013.05.032. Epub 2013 May 29.

●● Enlace al texto completo (gratis o de pago)

1016/j.bbagen.2013.05.032

AUTORES / AUTHORS: - Kavitha K; Kowshik J; Kishore TK; Baba AB; Nagini S

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India.

RESUMEN / SUMMARY: - BACKGROUND: The oncogenic transcription factors NF-kappaB and beta-catenin, constitutively activated by upstream serine/threonine kinases control several cellular processes implicated in malignant transformation including apoptosis evasion. The aim of this study was to investigate the chemopreventive effects of astaxanthin, an antioxidant carotenoid, in the hamster buccal pouch (HBP) carcinogenesis model based on its ability to modulate NF-kappaB and Wnt signaling pathways and induce apoptosis. METHODS: We determined the effect of dietary supplementation of astaxanthin on the oncogenic signaling pathways - NF-kappaB and Wnt/beta-catenin, their upstream activator kinases - Erk/MAPK and PI-3K/Akt, and the downstream event - apoptosis evasion by real-time quantitative RT-PCR, western blot, and immunohistochemical analyses. RESULTS: We found that astaxanthin inhibits NF-kappaB and Wnt signaling by downregulating the key regulatory enzymes IKKbeta and GSK-3beta. Analysis of gene expression and docking interactions revealed that inhibition of these pathways may be mediated via inactivation of the upstream signaling kinases Erk/Akt by astaxanthin. Astaxanthin also induced caspase-mediated mitochondrial apoptosis by downregulating the expression of antiapoptotic Bcl-2, p-Bad, and survivin and upregulating proapoptotic Bax and Bad, accompanied by efflux of Smac/Diablo and cytochrome-c into the cytosol, and induced cleavage of poly (ADP-ribose) polymerase (PARP). CONCLUSIONS: The results provide compelling evidence that astaxanthin exerts chemopreventive effects by concurrently inhibiting phosphorylation of transcription factors and signaling kinases and inducing intrinsic apoptosis. GENERAL SIGNIFICANCE: Astaxanthin targets key molecules in oncogenic signaling pathways and induces apoptosis and is a promising candidate agent for cancer prevention and therapy.

[778]

TÍTULO / TITLE: - Novel therapeutic approach of Ph-positive leukemia: combination of tyrosine kinase inhibitors with other targeted drugs.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Rinsho Ketsueki. 2013 Jun;54(6):559-67.

AUTORES / AUTHORS: - Tauchi T

[779]

TÍTULO / TITLE: - Sulindac and Celecoxib Regulate Cell Cycle Progression by p53/p21 Up Regulation to Induce Apoptosis During Initial Stages of Experimental Colorectal Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Biochem Biophys. 2013 Jul 16.

●● Enlace al texto completo (gratis o de pago) [1007/s12013-013-9711-](#)

[8](#)

AUTORES / AUTHORS: - Vaish V; Rana C; Piplani H; Vaiphei K; Sanyal SN

INSTITUCIÓN / INSTITUTION: - Department of Biophysics, Basic Medical Science Building, Panjab University, Chandigarh, 160014, India.

RESUMEN / SUMMARY: - In the present study we have elaborated the putative mechanisms could be followed by the non-steroidal anti-inflammatory drugs (NSAIDs) viz. Sulindac and Celecoxib in the regulation of cell cycle checkpoints along with tumor suppressor proteins to achieve their chemopreventive effects in the initial stages of experimental colorectal cancer. Male Sprague-Dawley rats were administered with 1,2-dimethylhydrazine dihydrochloride (DMH) to produce early stages of colorectal carcinogenesis. The mRNA expression profiles of various target genes were analyzed by RT-PCR and validated by quantitative real-time PCR, whereas protein expression was analyzed by Western blotting. Nuclear localization of transcription factors or other nuclear proteins was analyzed by electrophoretic mobility shift assay and immunofluorescence. Flowcytometry was performed to analyze the differential apoptotic events and cell cycle regulation. Molecular docking studies with different target proteins were also performed to deduce the various putative mechanisms of action followed by Sulindac and Celecoxib. We observed that DMH administration has abruptly increased the proliferation of colonic cells which is macroscopically visible in the form of multiple plaque lesions and correlates with the disturbed molecular mechanisms of cell cycle regulation. However, co-administration of NSAIDs has shown regulatory effects on cell cycle checkpoints via induction of various tumor suppressor proteins. We may conclude that Sulindac and Celecoxib could possibly follow p53/p21 mediated regulation of cell proliferation, where down regulation of NF-kappaB signaling and activation of PPARgamma might serve as important additional events in vivo.

[780]

TÍTULO / TITLE: - Uterine artery pulsatility index improves prediction of methotrexate resistance in women with gestational trophoblastic neoplasia with FIGO score 5-6.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BJOG. 2013 Jul;120(8):1012-5. doi: 10.1111/1471-0528.12196. Epub 2013 Mar 21.

●● Enlace al texto completo (gratis o de pago) 1111/1471-0528.12196

AUTORES / AUTHORS: - Sita-Lumsden A; Medani H; Fisher R; Harvey R; Short D; Sebire N; Savage P; Lim A; Seckl MJ; Agarwal R

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Charing Cross Gestational Trophoblastic Disease Centre, Charing Cross Hospital, London, UK.

RESUMEN / SUMMARY: - **OBJECTIVE:** The Uterine Artery Pulsatility Index (UAPI) is an ultrasound measure of tumour vascularity. In this study, we hypothesised that a UAPI ≤ 1 (high vascularity) would identify women with gestational trophoblastic neoplasia (GTN) at increased risk of resistance to first-line single-agent methotrexate (MTX-R). **DESIGN:** Single-centre cohort study. **SETTING:** Charing Cross Hospital, a UK national centre for the treatment of trophoblastic disease. **POPULATION:** All women with a GTN FIGO score 5-6 treated with methotrexate (n = 92), between 1999 and 2011, at Charing Cross Hospital. **METHODS:** UAPI was measured before the start of chemotherapy, and women were monitored for the development of MTX-R. **MAIN OUTCOME MEASURES:** Frequency of MTX-R in women with UAPI ≤ 1 compared with UAPI >1 . **RESULTS:** UAPI was measured before chemotherapy in 73 of 92 women with GTN FIGO score 5-6. UAPI ≤ 1 predicted MTX-R independent of the FIGO score (hazard ratio 2.9, P = 0.04), with an absolute risk of MTX-R in women with a UAPI ≤ 1 of 67% (95% CI 53-79%) compared with 42% (95% CI 24-61%) with a UAPI >1 (P = 0.036). **CONCLUSION:** Our results suggest UAPI is an independent predictor of MTX-R in women with FIGO 5-6 GTN.

[781]

TÍTULO / TITLE: - In vitro targeting of Polo-like kinase 1 in bladder carcinoma: Comparative effects of four potent inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jul 1;14(7):648-57. doi: 10.4161/cbt.25087. Epub 2013 May 31.

●● Enlace al texto completo (gratis o de pago) 4161/cbt.25087

AUTORES / AUTHORS: - Brassesco MS; Pezuk JA; Morales AG; Carvalho de Oliveira J; Roberto GM; Nicioli da Silva G; Francisco de Oliveira H; Scrideli CA; Tone LG

INSTITUCIÓN / INSTITUTION: - Division of Pediatric Oncology; Department of Pediatrics; University of Sao Paulo; Sao Paulo, Brazil.

RESUMEN / SUMMARY: - Despite the improvements in neoadjuvant chemotherapy, the outcome of patients with advanced bladder cancer has changed very little over the past 30 years. In the present study we tested and compared the in vitro antitumor activities of four different inhibitors of Polo-like kinase 1 (PLK1) (BI 2536, BI 6727, GW843682X, and GSK461364), against 3 bladder carcinoma cell lines RT4, 5637 and T24. The impact on radiosensitivity and drug interactions in simultaneous treatments with cisplatin, methotrexate,

and doxorubicin were also investigated. Our results showed that PLK1 inhibition prevented cell proliferation and clonogenicity, causing significant inhibition of invasion of tumor cells, though modest differences were observed between drugs. Moreover, all PLK1 inhibitors induced G 2/M arrest, with the subsequent induction of death in all 3 cell lines. Drug interactions studies showed auspicious results for all PLK1 inhibitors when combined with the commonly used cisplatin and methotrexate, though combinations with doxorubicin showed mostly antagonistic effects. Comparably, the four PLK1 inhibitors efficiently sensitized cells to ionizing radiation. Our findings demonstrate that irrespective of the inhibitor used, the pharmacological inhibition of PLK1 constrains bladder cancer growth and dissemination, providing new opportunities for future therapeutic intervention. However, further laboratorial and pre-clinical tests are still needed to corroborate the usefulness of using them in combination with other commonly used chemotherapeutic drugs.

[782]

TÍTULO / TITLE: - Emerging tyrosine kinase inhibitors for esophageal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Opin Emerg Drugs. 2013 Jun;18(2):219-30. doi: 10.1517/14728214.2013.805203.

●● Enlace al texto completo (gratis o de pago)

[1517/14728214.2013.805203](#)

AUTORES / AUTHORS: - Ku GY; Ilson DH

INSTITUCIÓN / INSTITUTION: - Memorial Sloan-Kettering Cancer Center, Department of Medicine, Gastrointestinal Oncology Service, 300 East 66th Street, New York, NY 10065, USA.

RESUMEN / SUMMARY: - INTRODUCTION: Because of the poor prognosis for patients with esophagogastric cancers (EGCs), increasing attention has focused on targeted agents. AREAS COVERED: Targets include epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), Her2, mammalian target of rapamycin (mTOR), and MET. We briefly discuss preclinical data and the rationale for targeting these pathways and summarize the results of clinical trials of tyrosine kinase inhibitors (TKIs) against these targets. EXPERT OPINION: While anti-EGFR therapy has been extensively investigated, completed Phase III trials suggest that this is not a promising target. A Phase III trial of an anti-VEGF antibody failed to show improvement in the primary endpoint of overall survival but response rates and progression-free survival were improved; a Phase III trial of an anti-VEGF receptor 2 antibody in second-line therapy did show improved survival. As such, Phase II and III evaluations of anti-VEGF TKIs are ongoing. The only Food and Drug Administration-approved targeted therapy in EGC is trastuzumab, an anti-Her2 antibody, and the results of a Phase III evaluation of lapatinib, an anti-Her2 TKI,

are awaited. Phase III evaluation of an mTOR inhibitor has been negative. Finally, MET inhibition appears to have significant clinical potential and early testing of MET TKIs is underway.

[783]

TÍTULO / TITLE: - Hexokinase II in breast carcinoma: a potent prognostic factor associated with hypoxia-inducible factor 1alpha and Ki-67.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Sci. 2013 Jul 19. doi: 10.1111/cas.12238.

●● [Enlace al texto completo \(gratis o de pago\) 1111/cas.12238](#)

AUTORES / AUTHORS: - Sato-Tadano A; Suzuki T; Amari M; Takagi K; Miki Y; Tamaki K; Watanabe M; Ishida T; Sasano H; Ohuchi N

INSTITUCIÓN / INSTITUTION: - Departments of Surgical Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan.

RESUMEN / SUMMARY: - Hypoxia-inducible factor 1alpha (HIF-1alpha) mediates adaptive responses to changes under tissue hypoxia in carcinoma cells through controlling the expression of various target genes. Previous studies demonstrated that HIF-1alpha was associated with adverse clinical outcome in the breast carcinoma patients, but its details have remained largely unknown. Therefore, in this study, we first examined expression profiles of HIF-1alpha-induced genes in 10 breast carcinoma cases using microarray data and demonstrated that the status of hexokinase II (HKII) was associated with recurrence of the patients among these genes. HKII is an enzyme involved in the first and rate-limiting step of glycolysis, but its clinical significance has not yet been examined in breast carcinoma. Therefore, we further immunolocalized HKII in 118 breast carcinomas. HKII immunoreactivity was detected in 44% of the cases, and significantly associated with histological grade, Ki-67 labeling index and HIF-1alpha immunoreactivity. HKII status was also significantly associated with increased risk of recurrence and adverse clinical outcome in breast cancer patients. Moreover, subsequent multivariate analysis did demonstrate that HKII status was an independent prognostic factor for disease-free survival of the patients. These results all suggest that HKII is induced by HIF-1alpha and plays important roles in the proliferation and/or progression of breast carcinoma possibly through increased glycolytic activity. HKII status is therefore considered a potent prognostic factor in human breast cancer patients. This article is protected by copyright. All rights reserved.

[784]

TÍTULO / TITLE: - Glycolysis inhibition sensitizes non-small cell lung cancer with T790M mutation to irreversible EGFR inhibitors via translational suppression of Mcl-1 by AMPK activation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jul 24.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-12-1188](http://dx.doi.org/10.1158/1535-7163.MCT-12-1188)

AUTORES / AUTHORS: - Kim SM; Yun MR; Hong YK; Solca F; Kim JH; Kim HJ; Cho BC

INSTITUCIÓN / INSTITUTION: - 1Brain Korea 21 Project for Medical Sciences, Yonsei University College of Medicine.

RESUMEN / SUMMARY: - The secondary epidermal growth factor receptor (EGFR) T790M is the most common mechanism of resistance to reversible EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. Although afatinib (BIBW2992), a second-generation irreversible EGFR TKI, was expected to overcome the acquired resistance, it showed limited efficacy in a recent phase III clinical study. In this study, we found that the inhibition of glycolysis using 2-deoxy-D-glucose (2DG) improves the efficacy of afatinib in H1975 and PC9-GR NSCLC cells with EGFR T790M. Treatment with the combination of 2DG and afatinib induced intracellular ATP depletion in both H1975 and PC9-GR cells, resulting in activation of AMP-activated protein kinase (AMPK). AMPK activation played a central role in the cytotoxicity of the combined treatment with 2DG and afatinib through the inhibition of mammalian target of rapamycin (mTOR). The alteration of the AMPK/mTOR signaling pathway by the inhibition of glucose metabolism induced specific downregulation of Mcl-1, a member of anti-apoptotic Bcl-2 family, through the translational control. The enhancement of afatinib sensitivity by 2DG was confirmed in in vivo PC9-GR xenograft model. In conclusion, this study examined whether the inhibition of glucose metabolism using 2DG enhances the sensitivity to afatinib in NSCLC cells with EGFR T790M through the regulation of AMPK/mTOR/Mcl-1 signaling pathway. These data suggest that the combined use of an inhibitor of glucose metabolism and afatinib is a potential therapeutic strategy for the treatment of patients with acquired resistance to reversible EGFR TKIs due to secondary EGFR T790M.

[785]

TÍTULO / TITLE: - Gastric cancer pharmacogenetics: progress or old tripe?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenomics. 2013 Jul;14(9):1053-64. doi: 10.2217/pgs.13.88.

●● Enlace al texto completo (gratis o de pago) [2217/pgs.13.88](http://dx.doi.org/10.2217/pgs.13.88)

AUTORES / AUTHORS: - Patel JN; Fuchs CS; Owzar K; Chen Z; McLeod HL

INSTITUCIÓN / INSTITUTION: - UNC Institute for Pharmacogenomics & Individualized Therapy, University of North Carolina, 120 Mason Farm Road, CB #7361, Room 1010, Chapel Hill, NC 27599-7361, USA.

RESUMEN / SUMMARY: - Gastric cancer remains the second most frequent cause of cancer-related mortality. While surgery is traditionally the initial treatment for

early-stage disease, the addition of chemotherapy has been shown to significantly increase overall survival and progression-free survival in advanced and metastatic stages of disease. However, despite the incorporation of newer chemotherapies and regimens into gastric cancer clinical trials, the response rate and median overall survival for treated patients has not significantly improved throughout the years; therefore, newer therapeutic approaches to improve upon the medication selection process are warranted. Treatment and dose selection based on patient factors, such as genetic variation, may provide a more rational and potentially more powerful means of personalizing chemotherapy. This review provides an update on the current status of pharmacogenetic studies regarding germline DNA mutations that may alter response to chemotherapeutic agents used to treat gastric cancer, including perspectives on clinical translation and future work.

[786]

TÍTULO / TITLE: - Inhibition of glioma growth by minocycline is mediated through endoplasmic reticulum stress-induced apoptosis and autophagic cell death.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neuro Oncol. 2013 Jun 20.

●● Enlace al texto completo (gratis o de pago) [1093/neuonc/not073](#)

AUTORES / AUTHORS: - Liu WT; Huang CY; Lu IC; Gean PW

INSTITUCIÓN / INSTITUTION: - Institute of Basic Medical Sciences (W.-T.L., P.-W.G.); Department of Pharmacology, (W.-T.L., I.-C.L., P.-W.G.); Division of Neurosurgery, Department of Surgery, National Cheng-Kung University Hospital, Tainan, Taiwan (C.-Y.H.).

RESUMEN / SUMMARY: - Background We have reported that minocycline (Mino) induced autophagic death in glioma cells. In the present study, we characterize the upstream regulators that control autophagy and switch cell death from autophagic to apoptotic. Methods Western blotting and immunofluorescence were used to detect the expressions of eukaryotic translation initiation factor 2alpha (eIF2alpha), transcription factor GADD153 (CHOP), and glucose-regulated protein 78 (GRP78). Short hairpin (sh)RNA was used to knock down eIF2alpha or CHOP expression. Autophagy was assessed by the conversion of light chain (LC)3-I to LC3-II and green fluorescent protein puncta formation. An intracranial mouse model and bioluminescent imaging were used to assess the effect of Mino on tumor growth and survival time of mice. Results The expression of GRP78 in glioma was high, whereas in normal glia it was low. Mino treatment increased GRP78 expression and reduced binding of GRP78 with protein kinase-like endoplasmic reticulum kinase. Subsequently, Mino increased eIF2alpha phosphorylation and CHOP expression. Knockdown of eIF2alpha or CHOP reduced Mino-induced LC3-II conversion and glioma cell death. When autophagy was inhibited, Mino induced cell death in a caspase-dependent manner. Rapamycin in combination with Mino produced synergistic effects on

LC3 conversion, reduction of the Akt/mTOR/p70S6K pathway, and glioma cell death. Bioluminescent imaging showed that Mino inhibited the growth of glioma and prolonged survival time and that these effects were blocked by shCHOP. Conclusions Mino induced autophagy by eliciting endoplasmic reticulum stress response and switched cell death from autophagy to apoptosis when autophagy was blocked. These results coupled with clinical availability and a safe track record make Mino a promising agent for the treatment of malignant gliomas.

[787]

TÍTULO / TITLE: - Lymph node ratio is a critical prognostic predictor in gastric cancer treated with S-1 chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Gastric Cancer. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1007/s10120-013-0253-](#)

[y](#)

AUTORES / AUTHORS: - Ema A; Yamashita K; Sakuramoto S; Wang G; Mieno H; Nemoto M; Shibata T; Katada N; Kikuchi S; Watanabe M

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Kitasato University School of Medicine, Sagami-hara, Japan.

RESUMEN / SUMMARY: - BACKGROUND: S-1 is an oral anticancer drug widely used in postoperative adjuvant therapy for patients in Japan with stage II/III gastric cancer. Candidates for more intense adjuvant treatments need to be identified, particularly among patients with stage III cancer. METHODS: Univariate and multivariate analyses were conducted for patients with stage II/III gastric cancer who underwent surgery and received S-1 postoperatively between 2000 and 2010. RESULTS: Factors indicating poor prognosis identified by univariate analysis include male sex ($P = 0.022$), age ≥ 67 years ($P = 0.021$), intestinal-type histology ($P = 0.049$), lymph node ratio $\geq 16.7\%$ ($P < 0.0001$), open surgery ($P = 0.039$), as well as the 13th JGCA stage ($P < 0.0001$) and the 14th JGCA/7th International Union Against Cancer (UICC) stage ($P < 0.0001$). Multivariate analysis revealed that lymph node ratio $\geq 16.7\%$ and intestinal-type histology were significant as predictors of prognosis, independent from the pathological stages. Based on these and other findings, stage IIIc cancer on the 14th JGCA/7th UICC stage system in combination with the lymph node ratio could identify patients with extremely high risk for recurrence. CONCLUSIONS: Our current findings suggest that lymph node ratio $\geq 16.7\%$ in combination with the new staging system could be a useful prognostic indicator in advanced gastric cancer. Because these high-risk patients cannot be identified preoperatively by any diagnostic tool, further improvement in postoperative adjuvant therapy is warranted.

[788]

TÍTULO / TITLE: - Sulindac selectively inhibits colon tumor cell growth by activating the cGMP/PKG pathway to suppress Wnt/beta-catenin signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Cancer Ther. 2013 Jun 26.

●● Enlace al texto completo (gratis o de pago) [1158/1535-7163.MCT-13-0048](#)

AUTORES / AUTHORS: - Li N; Xi Y; Tinsley HN; Gurpinar E; Gary BD; Zhu B; Li Y; Chen X; Keeton AB; Abadi AH; Moyer MP; Grizzle WE; Chang WC; Clapper ML; Piazza GA

INSTITUCIÓN / INSTITUTION: - 1Department of Biochemistry and Molecular Genetics, University of Alabama in Birmingham.

RESUMEN / SUMMARY: - NSAIDs display promising antineoplastic activity for colorectal and other cancers, but toxicity from cyclooxygenase (COX) inhibition limits their long-term use for chemoprevention. Previous studies have concluded that the basis for their tumor cell growth inhibitory activity does not require COX inhibition, although the underlying mechanism is poorly understood. Here we report that the NSAID, sulindac sulfide (SS) inhibits cyclic guanosine monophosphate phosphodiesterase (cGMP PDE) activity to increase intracellular cGMP levels and activate cGMP dependent protein kinase (PKG) at concentrations that inhibit proliferation and induce apoptosis of colon tumor cells. SS did not activate the cGMP/PKG pathway, nor affect proliferation or apoptosis in normal colonocytes. Knockdown of the cGMP-specific PDE5 isozyme by siRNA and PDE5-specific inhibitors, tadalafil and sildenafil, also selectively inhibited the growth of colon tumor cells that expressed high levels of PDE5 compared with colonocytes. The mechanism by which SS and the cGMP/PKG pathway inhibits colon tumor cell growth appears to involve the transcriptional suppression of beta-catenin to inhibit Wnt/beta-catenin TCF transcriptional activity, leading to down-regulation of cyclin D1 and survivin. These observations suggest that safer and more efficacious sulindac derivatives can be developed for colorectal cancer chemoprevention by targeting PDE5 and possibly other cGMP degrading isozymes.

[789]

TÍTULO / TITLE: - Clinical Outcomes and Prognostic Factors Associated with the Response to Erlotinib in Non-Small-Cell Lung Cancer Patients with Unknown EGFR Mutational Status.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(5):3255-61.

AUTORES / AUTHORS: - Aydiner A; Yildiz I; Seyidova A

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Istanbul University Institute of Oncology, Istanbul, Turkey E-mail : dr_ibrahim2000@yahoo.com.

RESUMEN / SUMMARY: - Background: The efficacy of erlotinib is controversial in patients with unknown EGFR mutational status. The aim of this study was to identify the clinicopathological factors that are predictive of erlotinib treatment outcomes for NSCLC patients with unknown EGFR mutational status. Materials and Methods: A retrospective analysis of 109 patients with advanced NSCLC who had previously failed at least one line of chemotherapy and received subsequent treatment with erlotinib (150 mg/day orally) was performed. A Cox proportional hazard model for univariate and multivariate analyses was used to identify the baseline clinical parameters correlating with treatment outcome, expressed in terms of hazard ratios (HRs) and 95% confidence intervals. Results: The median treatment duration was 15 weeks (range, 4-184). The disease control rate was 55%, including disease stability for ≥ 3 months for 40% of the patients. Median progression-free survival and median overall survival (OS) were 4.2 and 8.5 months, respectively. The Cox model indicated that an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 (HR 3.82; $p < 0.001$), presence of intra-abdominal metastasis (HR 3.42; $p = 0.002$), 2 or more prior chemotherapy regimens (HR 2.29; $p = 0.021$), and weight loss $> 5\%$ (HR 2.05; $p = 0.034$) were independent adverse prognostic factors for OS in NSCLC patients treated with erlotinib. Conclusions: This study suggests that NSCLC patients should be enrolled in erlotinib treatment after a first round of unsuccessful chemotherapy to improve treatment success, during which they should be monitored for intra-abdominal metastasis and weight loss.

[790]

TÍTULO / TITLE: - Validation of Circulating miRNA Biomarkers for Predicting Lymph Node Metastasis in Gastric Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Diagn. 2013 Jun 24. pii: S1525-1578(13)00096-2. doi: 10.1016/j.jmoldx.2013.04.004.

●● Enlace al texto completo (gratis o de pago)

1016/j.jmoldx.2013.04.004

AUTORES / AUTHORS: - Kim SY; Jeon TY; Choi CI; Kim DH; Kim DH; Kim GH; Ryu DY; Lee BE; Kim HH

INSTITUCIÓN / INSTITUTION: - Department of Clinical Laboratory Medicine, Pusan National University School of Medicine and Medical Research Institute, Busan, South Korea.

RESUMEN / SUMMARY: - We validated candidate biomarkers using circulating miRNAs by analyzing serum miRNA concentrations from patients with gastric cancer (GC) to predict lymph node (LN) metastasis. In a pilot study, serum levels of miR-21, miR-27^a, miR-106b, miR-146^a, miR-148^a, miR-223, and miR-433 were compared in 10 healthy donors, 16 LN-positive patients with GC, and 15 LN-negative patients with GC. Then, we compared the level of three miRNAs (miR-21, miR-146^a, and miR-148^a) with the total of 79 GC patients with or

without LN metastasis. In the pilot study, miR-21, miR-27^a, miR-106b, miR-146^a, miR-148^a, and miR-223 concentrations from LN-positive patients with GC were significantly different from those of LN-negative patients with GC (P < 0.001, P = 0.003, P = 0.033, P < 0.001, P < 0.001, and P = 0.017, respectively). In the validation study, levels of miR-21, miR-146^a, and miR-148^a increased as pN stage increased (P < 0.001, P = 0.001, and P < 0.001, respectively). Levels of the miRNAs were significantly different between pN0 and pN1 in the pT1 group (P = 0.013, P = 0.004, and P = 0.035, respectively) and among clinical stages (P = 0.001, P = 0.002, and P < 0.001, respectively). No differences in miRNA levels were observed by pT stage, Lauren's classification, sex, or age. Serum concentrations of miR-21, miR-146^a, and miR-148^a were closely associated with GC pN stage. These serum miRNA levels could be biomarker candidates to predict the presence of LN metastasis.

[791]

TÍTULO / TITLE: - Gefitinib selectively inhibits tumor cell migration in EGFR-amplified human glioblastoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neuro Oncol. 2013 Aug;15(8):1048-57. doi: 10.1093/neuonc/not053. Epub 2013 Jun 7.

●● [Enlace al texto completo \(gratis o de pago\) 1093/neuonc/not053](#)

AUTORES / AUTHORS: - Parker JJ; Dionne KR; Massarwa R; Klaassen M; Foreman NK; Niswander L; Canoll P; Kleinschmidt-Demasters BK; Waziri A

INSTITUCIÓN / INSTITUTION: - Corresponding Author: Allen Waziri, MD, Department of Neurosurgery, Academic Office Building One, Rm. 5001, 12631 E 17th Ave., Aurora, CO 80045. allen.waziri@ucdenver.edu.

RESUMEN / SUMMARY: - Background Tissue invasion is a hallmark of most human cancers and remains a major source of treatment failure in patients with glioblastoma (GBM). Although EGFR amplification has been previously associated with more invasive tumor behavior, existing experimental models have not supported quantitative evaluation of interpatient differences in tumor cell migration or testing of patient-specific responses to therapies targeting invasion. To explore these questions, we optimized an ex vivo organotypic slice culture system allowing for labeling and tracking of tumor cells in human GBM slice cultures. Methods With use of time-lapse confocal microscopy of retrovirally labeled tumor cells in slices, baseline differences in migration speed and efficiency were determined and correlated with EGFR amplification in a cohort of patients with GBM. Slices were treated with gefitinib to evaluate anti-invasive effects associated with targeting EGFR. Results Migration analysis identified significant patient-to-patient variation at baseline. EGFR amplification was correlated with increased migration speed and efficiency compared with nonamplified tumors. Critically, gefitinib resulted in a selective and significant reduction of tumor cell migration in EGFR-amplified tumors. Conclusions These

data provide the first identification of patient-to-patient variation in tumor cell migration in living human tumor tissue. We found that EGFR-amplified GBM are inherently more efficient in their migration and can be effectively targeted by gefitinib treatment. These data suggest that stratified clinical trials are needed to evaluate gefitinib as an anti-invasive adjuvant for patients with EGFR-amplified GBM. In addition, these results provide proof of principle that primary slice cultures may be useful for patient-specific screening of agents designed to inhibit tumor invasion.

[792]

TÍTULO / TITLE: - Neem leaf glycoprotein is superior than Cisplatin and Sunitinib malate in restricting melanoma growth by normalization of tumor microenvironment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int Immunopharmacol. 2013 Sep;17(1):42-9. doi: 10.1016/j.intimp.2013.05.005. Epub 2013 Jun 5.

- Enlace al texto completo (gratis o de pago)

1016/j.intimp.2013.05.005

AUTORES / AUTHORS: - Barik S; Bhuniya A; Banerjee S; Das A; Sarkar M; Paul T; Ghosh T; Ghosh S; Roy S; Pal S; Bose A; Baral R

INSTITUCIÓN / INSTITUTION: - Department of Immunoregulation and Immunodiagnosics, Chittaranjan National Cancer Institute (CNCI), 37, S. P. Mukherjee Road, Kolkata 700026, India.

RESUMEN / SUMMARY: - We have observed earlier that therapeutic treatment with neem leaf glycoprotein (NLGP) inhibits murine B16-melanoma growth in vivo and improves survivability of treated mice. Anti-tumor effect of NLGP is directly associated with enhanced CD8(+) T cell activity and downregulation of suppressive cellular functions. Objective of this present study is to know the efficacy of NLGP in comparison to two popular drugs, Cisplatin and Sunitinib malate (Sutent) in relation to the modulation of tumor microenvironment (TME). Analysis of cytokine milieu within TME revealed IL-10, TGFbeta, IL-6 rich type 2 characters was significantly switched to type 1 microenvironment with dominance of IFNgamma and IL-2 within NLGP-TME, which was not found in other cases; however Cisplatin-TME appeared better in type 2 to type 1 conversion than Sutent-TME as evidenced by RT-PCR, ELISA and immunohistochemical analysis. NLGP-TME educated CD8(+) T cells exhibited greater cytotoxicity to B16 Melanoma cells in vitro and these cells showed comparatively higher expression of cytotoxicity related molecules, perforin and granzyme B than Cisplatin-TME and Sutent-TME educated T cells. Adoptive transfer of NLGP-TME exposed T cells, but not PBS-TME exposed cells in mice, is able to significantly inhibit the growth of melanoma in vivo. Such tumor growth inhibition was in significantly lower extent when therapeutic CD8(+) T cells were exposed to either Cisplatin-TME or Sutent-TME or control-TME.

Accumulated evidences strongly suggest that non toxic NLGP normalized TME allows T cells to perform optimally than other TMEs under study to inhibit the melanoma growth.

[793]

TÍTULO / TITLE: - Antitumor and modeling studies of a penetratin-peptide that targets E2F-1 in small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Biol Ther. 2013 Jun 3;14(8).

AUTORES / AUTHORS: - Xie X; Kerrigan JE; Minko T; Garbuzenko O; Lee KC; Scarborough A; Abali EE; Budak-Alpdogan T; Johnson-Farley N; Banerjee D; Scotto KW; Bertino JR

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology and Medicine; Cancer Institute of New Jersey; Robert Wood Johnson Medical School; UMDNJ; New Brunswick, NJ USA.

RESUMEN / SUMMARY: - E2F-1, a key transcription factor necessary for cell growth, DNA repair and differentiation, is an attractive target for development of anticancer drugs in tumors that are E2F “oncogene addicted.” We identified a peptide isolated from phage clones that bound tightly to the E2F-1 promoter consensus sequence. The peptide was coupled to penetratin to enhance cellular uptake. Modeling of the penetratin-peptide (PEP) binding to the DNA E2F-1 promoter demonstrated favorable interactions that also involved the participation of most of the penetratin sequence. The penetratin-peptide (PEP) demonstrated potent in vitro cytotoxic effects against a range of cancer cell lines, particularly against Burkitt lymphoma cells and Small Cell Lung Cancer (SCLC) cells. Further studies in the H-69 SCLC cell line showed that the PEP inhibited transcription of E2F-1 and also several important E2F-regulated enzymes involved in DNA synthesis, namely, thymidylate synthase, thymidine kinase and ribonucleotide reductase. As the PEP was found to be relatively unstable in serum, it was encapsulated in PEGylated liposomes for in vivo studies. Treatment of mice bearing the human small cell lung carcinoma H-69 with the PEP encapsulated in PEGylated liposomes caused tumor regression without significant toxicity. The liposome encapsulated PEP has promise as an antitumor agent, alone or in combination with inhibitors of DNA synthesis.

[794]

TÍTULO / TITLE: - Pegylated interferon-alpha2b and ribavirin decrease claudin-1 and E-cadherin expression in HepG2 and Huh-7.5 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Ann Hepatol. 2013 Jul-Aug;12(4):616-25.

AUTORES / AUTHORS: - Rendon-Huerta EP; Torres-Martinez A; Charles-Nino C; Rivas-Estilla AM; Paez A; Fortoul TI; Montano LF

INSTITUCIÓN / INSTITUTION: - Departamento de Biología Celular y Tisular, Facultad de Medicina, UNAM, Mexico, D.F. 04510, Mexico.

RESUMEN / SUMMARY: - Background. Hepatitis C virus (HCV) infection usually results in long-term viremia. Entry of HCV into the hepatocyte requires claudin-1, -6, -9 and occludin. The efficacy of Pegylated interferon-alpha (PEG-IFN) treatment against HCV infection increased when ribavirin (RBV) was added to the therapeutic scheme. Our aim was to investigate if PEG-IFN plus RBV regulate claudin expression. Material and methods. HepG2, Huh-7 and Huh-7.5 cells were treated with PEG-IFN-alpha2a or alpha2b and/or RBV at different times before obtaining the cytosolic, membrane and cytoskeletal fractions. Claudin-1, 3, 4, 6, and 9, E-cadherin and occludin expression was evaluated by Western blot analysis. Transepithelial electrical resistance (TER) was also determined. Results. Claudin-1, 3, 4, 6, E-cadherin and occludin are constitutively expressed mainly in HepG2 cell membrane. Claudin-1 and E-cadherin cell membrane expression diminished after exposure to PEGIFNalpha2b (50 ng) + RBV(50 mug); the maximal decrease was observed with 200 ng of PEG-IFNalpha2b + 200 mug of RBV. The effect was less intense with PEG-IFNalpha2a. The inhibition of claudin-1 and E-cadherin expression in Huh-7 and Huh-7.5 cells was only observed with 200 ng of PEG-IFNalpha2b + 200 mug of RBV. TER diminished marginally in the HCV containing hepatoma cells with 200 ng of PEG-IFNalpha2b + 200 mug of RBV. Claudin-1 mRNA expression level was not affected by the combined treatment. Conclusion. The increased therapeutic efficacy of the PEG-IFNalpha2b plus RBV treatment could be secondary to the inhibition of claudin-1 and E-cadherin cell membrane expression.

[795]

TÍTULO / TITLE: - Secretoglobin expression in ovarian carcinoma: lipophilin B gene upregulation as an independent marker of better prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Transl Med. 2013 Jul 2;11:162. doi: 10.1186/1479-5876-11-162.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-162](#)

AUTORES / AUTHORS: - Bignotti E; Tassi RA; Calza S; Ravaggi A; Rossi E; Donzelli C; Todeschini P; Romani C; Bandiera E; Zanotti L; Carnazza M; Quadraro F; Tognon G; Sartori E; Pecorelli S; Roque DM; Santin AD

INSTITUCIÓN / INSTITUTION: - Angelo Nocivelli Institute of Molecular Medicine, Division of Gynecologic Oncology, University of Brescia, Viale Europa 11, 25123 Brescia, Italy. bignottieliana@yahoo.it

RESUMEN / SUMMARY: - BACKGROUND: The aim of the present study was to investigate within ovarian carcinoma and normal ovarian biopsies the gene expression of multiple secretoglobin family members relative to mammaglobin B, which we previously reported as a promising novel ovarian carcinoma

prognostic marker. **METHODS:** Using quantitative real-time Reverse Transcription PCR we tested 53 ovarian carcinoma and 30 normal ovaries for the expression of 8 genes belonging to the secretoglobin family: mammaglobin A, lipophilin A, lipophilin B, uteroglobin, HIN-1, UGRP-1, RYD5 and IIS. Next, we decided to expand the LipB gene expression analysis to a further 48 ovarian carcinoma samples, for a total of 101 tumor tissues of various histologies and to study its protein expression by immunohistochemistry in formalin-fixed paraffin-embedded tumors and normal ovaries. Finally, we correlated lipophilin B gene and protein expression to conventional patient clinico-pathological features and outcome. **RESULTS:** We found significant mammaglobin A, lipophilin A, lipophilin B and RYD5 gene overexpression in ovarian carcinomas compared to normal ovaries. Lipophilin B mRNA showed a higher presence in tumors (75.4%) compared to normal ovaries (16.6%) and the most significant correlation with mammaglobin B mRNA ($r_s = 0.77$, $p < 0.001$). By immunohistochemical analysis, we showed higher lipophilin B expression in the cytoplasm of tumor cells compared to normal ovaries ($p < 0.001$). Moreover, lipophilin B gene overexpression was significantly associated with serous histology (serous vs clear cell $p = 0.027$; serous vs undifferentiated $p = 0.007$) and lower tumor grade ($p = 0.02$). Lower LipB mRNA levels (low versus high tertiles) were associated to a shorter progression-free ($p = 0.03$, HR = 2.2) and disease-free survival ($p = 0.02$, HR = 2.5) by univariate survival analysis and, importantly, they remain an independent prognostic marker for decreased disease-free ($p = 0.001$, HR = 3.9) and progression-free survival ($p = 0.004$, HR = 2.8) in multivariate Cox regression analysis. **CONCLUSIONS:** The present study represents the first quantitative evaluation of secretoglobin gene expression in normal and neoplastic ovarian tissues. Our results demonstrate lipophilin B gene and protein upregulation in ovarian carcinoma compared to normal ovary. Moreover, lipophilin B gene overexpression correlates with a less aggressive tumor phenotype and represents a novel ovarian carcinoma prognostic factor.

[796]

TÍTULO / TITLE: - A Case Series of Lengthy Progression-Free Survival With Pemetrexed-Containing Therapy in Metastatic Non-Small-Cell Lung Cancer Patients Harboring ROS1 Gene Rearrangements.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lung Cancer. 2013 Jun 27. pii: S1525-7304(13)00075-2. doi: 10.1016/j.clcc.2013.04.008.

●● Enlace al texto completo (gratis o de pago) 1016/j.clcc.2013.04.008

AUTORES / AUTHORS: - Riess JW; Padda SK; Bangs CD; Das M; Neal JW; Adrouny AR; Cherry A; Wakelee HA

INSTITUCIÓN / INSTITUTION: - Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA. Electronic address: riessjo@stanford.edu.

[797]

TÍTULO / TITLE: - Role of XRCC3, XRCC1 and XPD single-nucleotide polymorphisms in survival outcomes following adjuvant chemotherapy in early stage breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Transl Oncol. 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1007/s12094-013-1055-](http://dx.doi.org/10.1007/s12094-013-1055-8)

[8](#)

AUTORES / AUTHORS: - Castro E; Olmos D; Garcia A; Cruz JJ; Gonzalez-Sarmiento R

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Hospital Universitario de Salamanca, Paseo San Vicente, CP 37007, Salamanca, España, ecastromarcos@yahoo.es.

RESUMEN / SUMMARY: - INTRODUCTION: Anthracyclines have various mechanisms of action that in the end lead to DNA double-strand breaks. Single-nucleotide polymorphisms (SNPs) in DNA repair genes may alter the protein function, affecting DNA repair proficiency and, therefore, the efficiency of DNA damaging chemotherapy. We have analysed whether SNPs in DNA repair genes (XRCC1, XRCC3 and XPD) could be useful to predict the response to anthracyclines in patients with early-stage breast cancer (EBC). METHODS: Peripheral blood samples from 150 patients with EBC were used for genotyping XRCC3Thr241Met, XRCC1Arg399Gln and XPDlys751Gln. Genotypes were correlated with survival outcomes. RESULTS: Eighty-four patients received treatment with chemotherapy regimens containing anthracyclines. In this group, patients with XRCC1Arg399Arg had a significant improvement in 5-year Disease Free Survival (DFS) compared with those with the Arg/Gln and Gln/Gln variants (84 vs 46 %, $p = 0.026$). In the multivariate analysis, XRCC1Arg399Arg was reported as an independent prognostic factor for DFS (HR 0.4, CI-95 % 0.2-0.9, $p = 0.035$). Patients with the XRCC3 Met241Met genotype presented better 5-year OS than those carrying the Thr/Thr and Met/Thr variants (100 vs 70 %, $p = 0.030$). A multivariate analysis for OS confirmed the independent prognostic value of XRCC3 Met241Met (HR 0.15, CI-95 % 0.02-0.90, $p = 0.048$). These differences were not significant when patients receiving other chemotherapy treatments, different from anthracyclines, were also considered ($n = 150$). XPDlys751Lys was associated with older age at diagnosis than the Lys/Gln and Gln/Gln genotypes (65 vs 58 years, $p < 0.0001$). CONCLUSIONS: XRCC3Thr241Met and XRCC1Arg399Gln may be predictive of survival outcome in EBC patients treated with anthracycline-based chemotherapy regimens.

[798]

TÍTULO / TITLE: - CD44/CD24 as potential prognostic markers in node-positive invasive ductal breast cancer patients treated with adjuvant chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Mol Histol. 2013 Jul 9.

●● Enlace al texto completo (gratis o de pago) [1007/s10735-013-9523-](#)

[6](#)

AUTORES / AUTHORS: - Adamczyk A; Niemiec JA; Ambicka A; Mucha-Malecka A; Mitus J; Rys J

INSTITUCIÓN / INSTITUTION: - Department of Applied Radiobiology, Centre of Oncology, Maria Sklodowska-Curie Memorial Institute, Cracow Branch, Garncarska 11, 31-115, Krakow, Poland, aa.adamczyk@yahoo.com.

RESUMEN / SUMMARY: - The hypothesis on cancer stem cells assumes the existence of small subpopulation of cells that possess the ability to undergo self-renewal and can give rise to the diversity of differentiated cells that form the tumour. It has been accepted that CD44+/CD24-/low phenotype is one of the features characterizing breast cancer stem cells. The aim of our study was to assess (1) prognostic significance of CD44/CD24 expression as well as (2) a relation between the above-mentioned phenotype and breast cancer subtypes [based on estrogen (ER), progesterone receptors, human epidermal growth factor receptor 2 and Ki67 status] and expression of selected markers such as fascin, laminin-5 gamma-2 chain, cytokeratin (CK) 5/6 and 8/18, epidermal growth factor receptor (EGFR), smooth muscle actin, P-cadherin and lymphocytic infiltration in invasive ductal breast cancer patients (T >= 1, N >= 1, M0), who underwent mastectomy followed by chemotherapy (with taxanes and/or anthracyclines) or/and hormonotherapy. We noted that most cancers with CD44-/CD24- and CD44-/CD24+ phenotype were ER positive. The majority of CD44-/CD24-, CD44-/CD24+ and CD44+/CD24- tumours were characterized by CK5/6 and EGFR negativity. In univariate analysis we demonstrated that patients with pN1/pN2 and with CD44 +/CD24- carcinomas had significantly lower risk of progression or cancer-related death than those with pN3 or tumours characterised by other CD44/CD24 expression patterns. We also found 100 % DFS in 12 patients with CD44+/CD24-/CK5/6+/ER- phenotype. Other analysed parameters were insignificant. We conclude that tumours with immunophenotypes: CD44+/CD24- and CD44+/CD24-/CK5/6+/ER- might be more sensitive for chemotherapy based on taxanes and/or anthracyclines.

[799]

TÍTULO / TITLE: - Concurrent Infection of Hepatitis B Virus Negatively Affects the Clinical Outcome and Prognosis of Patients with Non-Hodgkin's Lymphoma after Chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 8;8(7):e69400. doi: 10.1371/journal.pone.0069400. Print 2013.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0069400](https://doi.org/10.1371/journal.pone.0069400)

AUTORES / AUTHORS: - Chen J; Wang J; Yang J; Zhang W; Song X; Chen L

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Changhai Hospital, Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - Hepatitis B virus (HBV) is hepatotropic and lymphotropic. HBV-infected individuals have an increased risk of developing malignant lymphoma, and the HBV infection rate in lymphoma patients is significantly higher than that in the general population. However, the exact mechanism and correlation between HBV infection and lymphoma onset and progression currently remain unclear. We retrospectively analyzed clinical data from non-Hodgkin's lymphoma (NHL) patients with different HBV infection statuses. The results showed that the HBV infection rate was significantly higher in patients with B-cell type and late stage of NHL. The chemotherapy efficacy for NHL patients with chronic active HBV infection was significantly lower than that for the patients with chronic inactive HBV infection, the patients with HBV carriers and the patients without HBV infection. In addition, the NHL chemotherapy activated HBV replication and caused significant liver dysfunction, which could further reduce the chemotherapy efficacy. Through Kaplan-Meier survival curve and log-rank analysis, we found that the HBV infection status in NHL patients was significantly correlated with the patients' progression-free survival (PFS) and overall survival (OS). Compared with the patients without HBV infection (PFS: 95% CI 47.915 to 55.640; OS: 95% CI 81.324 to 86.858), the PFS and OS of the patients with chronic active HBV infection were significantly shorter (PFS: 95% CI 9.424 to 42.589, $P < 0.001$; OS: 95% CI 42.840 to 82.259, $P = 0.006$). The study demonstrated that the sustained HBV replication in patients with chronic active HBV infection could be a key factor that influences the prognosis of NHL patients after chemotherapy, and thus may provide information for designing rational clinical treatments for NHL patients with different HBV infection statuses and improve the treatment efficacy and prognosis.

[800]

TÍTULO / TITLE: - Protein tyrosine kinase 6 is associated with nasopharyngeal carcinoma poor prognosis and metastasis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Transl Med. 2013 Jun 9;11:140. doi: 10.1186/1479-5876-11-140.

- Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-140](https://doi.org/10.1186/1479-5876-11-140)

AUTORES / AUTHORS: - Liu LN; Huang PY; Lin ZR; Hu LJ; Liang JZ; Li MZ; Tang LQ; Zeng MS; Zhong Q; Zeng BH

INSTITUCIÓN / INSTITUTION: - Department of Oncology, the Second Affiliated Hospital of Guangzhou medical college, 250 Changgang Road East, Guangzhou 510260, China. zhongqian@sysucc.org.cn.

RESUMEN / SUMMARY: - BACKGROUND: The aim of this study was to analyze the expression of protein tyrosine kinase 6 (PTK6) in nasopharyngeal carcinoma (NPC) samples, and to identify whether PTK6 can serve as a biomarker for the diagnosis and prognosis of NPC. METHODS: We used quantitative RT-PCR and Western blotting analysis to detect mRNA and protein expression of PTK6 in NPC cell lines and immortalized nasopharyngeal epithelial cell lines. 31 NPC and 16 non-tumorous nasopharyngeal mucosa biopsies were collected to detect the difference in the expression of mRNA level of PTK6 by quantitative RT-PCR. We also collected 178 NPC and 10 normal nasopharyngeal epithelial cases with clinical follow-up data to investigate the expression of PTK6 by immunohistochemistry staining (IHC). PTK6 overexpression on cell growth and colony formation ability were measured by the method of cell proliferation assay and colony formation assay. RESULTS: The expression of PTK6 was higher in most of NPC cell lines at both mRNA and protein levels than in immortalized nasopharyngeal epithelial cell lines (NPECs) induced by Bmi-1 (Bmi-1/NPEC1, and Bmi-1/NPEC2). The mRNA level of PTK6 was high in NPC biopsies compared to non-tumorous nasopharyngeal mucosa biopsies. IHC results showed the expression of PTK6 was significantly correlated to tumor size ($P < 0.001$), clinical stage ($P < 0.001$), and metastasis ($P = 0.016$). The patients with high-expression of PTK6 had a significantly poor prognosis compared to those of low-expression (47.8% versus 80.0%, $P < 0.001$), especially in the patients at the advanced stages (42.2% versus 79.1%, $P < 0.001$). Multivariate analysis indicated that the level of PTK6 expression was an independent prognostic factor for the overall survival of patients with NPC ($P < 0.001$). Overexpression of PTK6 in HNE1 cells enhanced the ability of cell proliferation and colony formation. CONCLUSIONS: Our results suggest that high-expression of PTK6 is an independent factor for NPC patients and it might serve as a potential prognostic biomarker for patients with NPC.

[801]

TÍTULO / TITLE: - Clinical significance of the thymidylate synthase, dihydropyrimidine dehydrogenase, and thymidine phosphorylase mRNA expressions in hepatocellular carcinoma patients receiving 5-fluorouracil-based transarterial chemoembolization treatment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jul 3;6:811-8. doi: 10.2147/OTT.S46498. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S46498](#)

AUTORES / AUTHORS: - Zhao H; Zhao Y; Guo Y; Huang Y; Lin S; Xue C; Xu F; Zhang Y; Zhao L; Hu Z; Zhang L

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China and National Anti-Cancer Drug Clinical Research Centre.

RESUMEN / SUMMARY: - PURPOSE: To determine whether 5-fluorouracil (5-FU) sensitivity is associated with the mRNA expressions of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and thymidine phosphorylase (TP) in patients with hepatocellular carcinoma (HCC) treated with 5-FU-based transarterial chemoembolization (TACE). METHODS: Formalin-fixed, paraffin-embedded tumor specimens from 40 patients treated with 5-FU-based TACE were selected for the examination of TS, DPD, and TP expression level by a quantitative real-time reverse transcription- polymerase chain reaction (PCR) technique. Patients were categorized into high and low expression groups according to the median expression level of each enzyme. Associations between the mRNA expression levels of TS, DPD, and TP and clinical parameters including treatment efficacies, clinicopathological factors, and prognosis were assessed. RESULTS: High DPD expression was associated with worse treatment outcome, including intrahepatic disease progression rate (hazard ratio [HR] for high DPD versus low DPD, 2.212; 95% confidence interval [CI], 1.030-4.753; P = 0.042), extrahepatic disease progression rate (HR for high versus low DPD, 3.171; 95% CI, 1.003-10.023; P = 0.049), and progression-free survival (HR for high versus low DPD, 2.308; 95% CI, 1.102-4.836; P = 0.027). No correlation was found between the mRNA expression of TS/TP and treatment outcome. CONCLUSION: DPD mRNA expression level was negatively correlated with the clinical outcomes of HCC patients treated with 5-FU-based TACE. These results provide indirect evidence that high DPD mRNA expression is a predictive marker of treatment resistance for 5-FU.

[802]

TÍTULO / TITLE: - Prognostic significance of estrogen receptor, progesterone receptor, HER2/neu, Ki-67, and nm23 expression in patients with invasive breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J BUON. 2013 Apr-Jun;18(2):359-65.

AUTORES / AUTHORS: - Cubukcu E; Kanat O; Fatih Olmez O; Kabul S; Canhoroz M; Avci N; Deligonul A; Hartavi M; Cubukcu S; Olmez F; Kurt E; Evrensel T; Gokgoz S; Manavoglu O

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Sevket Yilmaz Education and Research Hospital, Bursa, Turkey.

RESUMEN / SUMMARY: - Purpose: To determine the prognostic significance of estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki-67, and nm23 immunohistochemical expression with respect to progression free survival (PFS) and overall survival (OS) in Turkish patients with invasive breast cancer (IBC). Methods: Patients with IBC (n = 81; mean age = 51.9 +/- 11.1 years) were prospectively enrolled at the Department of Oncology, Uludag University Medical Center, Bursa, Turkey. Immunohistochemistry was performed on formalin- fixed, paraffin-embedded tissue sections. Results: We did not find any significant association between immunohistochemical expression of ER, PR,

HER2/ neu, Ki-67, and nm23 and the baseline characteristics of IBC patients. The median patient PFS was 30 months (range 22-45), and the median OS was 32 months (range 23-46). Stratification of the patient population according to nm23 immunohistochemical expression revealed a statistically significant difference in terms of both OS ($p < 0.05$) and DFS ($p < 0.05$). Multivariate Cox regression analysis indicated that tumor grade, axillary lymph node status, and nm23 immunohistochemical expression were the 3 main independent prognostic factors for PFS and OS in IBC patients. Conclusion: Reduced nm23 immunohistochemical expression is an independent negative prognostic factor for OS and PFS. Patients with negative nm23 expression may require a more intensive follow-up.

[803]

TÍTULO / TITLE: - Serum proteome predicts virological response in chronic hepatitis C genotype 1b patients treated with pegylated interferon plus ribavirin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Formos Med Assoc. 2013 Jun 26. pii: S0929-6646(13)00163-0. doi: 10.1016/j.jfma.2013.04.013.

●● Enlace al texto completo (gratis o de pago) 1016/j.jfma.2013.04.013

AUTORES / AUTHORS: - Yen YH; Wang JC; Hung CH; Lu SN; Wang JH; Hu TH; Kee KM; Hsiao CC; Lee CM

INSTITUCIÓN / INSTITUTION: - Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung University, College of Medicine, Kaohsiung, Taiwan; Graduate Institute of Clinical Medical Sciences, Chang Gung University, College of Medicine, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND/PURPOSE: Whether serum proteome changes can predict treatment response in chronic hepatitis C remains unclear. We investigated the association between serum proteome changes and virological responses in chronic hepatitis C virus genotype 1b (HCV-1b) patients treated with pegylated interferon (PegIFN) plus ribavirin (RBV). MATERIALS AND METHODS: One hundred and thirty-six HCV-1b patients who had completed a course of PegIFN plus RBV for 24 weeks, had a 24-week follow-up, and had pretreatment serum available were enrolled. These patients were divided into training and validation groups. We used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) for peptide profiling and ClinPro Tools version 2.0 bioinformatics software for data analysis. RESULTS: Seventy-four patients (54%) had a sustained virological response (SVR), whereas 62 did not. We identified three protein peaks in pretreatment sera where the expression levels significantly differed between SVR and non-SVR ($p < 0.05$). Using the class prediction tool composed of the three protein peaks, we were able to correctly predict SVR in 95% of validation group patients with sensitivity = 95%, specificity = 56.3%, positive predictive value = 73.1%, and negative predictive value = 90%. We also identified a set of 20 protein peaks where the expression levels significantly differed in

pretreatment sera between patients with nonresponse (NR) and virological response (SVR plus relapse; $p < 0.05$). Using the class prediction tool composed of these 20 protein peaks, we were able to correctly predict virological NR in 82% of validation group patients with sensitivity = 100%, specificity = 82%, positive predictive value = 92.6%, and negative predictive value = 100%. CONCLUSION: Pretreatment serum proteome allows prediction of SVR and NR to PegIFN plus RBV treatment in HCV-1b patients.

[804]

TÍTULO / TITLE: - Profile of BCR-ABL transcript levels based on Sokal prognostic score in chronic myeloid leukemia patients treated with imatinib.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Med Indones. 2013 Apr;45(2):107-13.

AUTORES / AUTHORS: - Ashariati A; Ugroseno S

INSTITUCIÓN / INSTITUTION: - Department Internal Medicine, Faculty of Medicine, Airlangga University-Dr. Soetomo Hospital, Surabaya, Indonesia.

amiashariati@yahoo.com

RESUMEN / SUMMARY: - AIM: to elucidate the pattern of molecular response assessed by logarithmic reduction in BCR-ABL transcription levels based on Sokal prognostic score in chronic phase chronic myeloid leukemia (CML) patients receiving Imatinib treatment. METHODS: cross-sectional study was conducted in the Hematologic Outpatient Clinic, Dr. Soetomo Hospital Surabaya in all chronic phase CML patients from June 2008 to June 2012. Data on subject characteristics (age and sex), complete blood count with differential and spleen size were collected. Patients were stratified according to Sokal score at diagnosis. Real-time quantitative PCR (RT-qPCR) were used to monitor BCR-ABL levels in patients who fulfilled study. Proportion difference of complete molecular response (MR) was analyzed by chi-square test, while differences of BCR-ABL transcript level among Sokal prognostic score subgroups was analyzed by Kruskal-Wallis test. RESULTS: 40 subjects finished the study. After 18 months of Imatinib treatment, the undetected BCR-ABL transcript level (complete MR) were 7(70%), 8(66.7%), and 9(50%) in low-, intermediate-, and high risk group patients, respectively ($p=0.417$). Although proportion of subjects with complete MR is higher in sokal low risk group compared to in sokal high risk groups (70% v.s. 50%), but this difference is not statistically significant ($p=0.557$). Kruskal-Wallis test showed that there was no significant difference of BCR-ABL transcript level among Sokal prognostic score subgroup ($p=0.734$). CONCLUSION: there was no difference of BCR-ABL transcript level among sokal prognostic score risk groups in chronic phase CML patients treated with Imatinib.

[805]

TÍTULO / TITLE: - Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 22;13:350. doi: 10.1186/1471-2407-13-350.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-350](#)

AUTORES / AUTHORS: - Lee S; Oh SY; Kim SH; Lee JH; Kim MC; Kim KH; Kim HJ

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Dong-A University College of Medicine, 3-1 Dongdaeshin-dong, Busan, Seo-gu 602-715, Korea. kimhj@dau.ac.kr.

RESUMEN / SUMMARY: - BACKGROUND: Several inflammatory response materials could be used for prediction of prognosis of cancer patients. The neutrophil lymphocyte ratio (NLR), and the platelet lymphocyte ratio (PLR) have been introduced for prognostic scoring system in various cancers. The objective of this study was to determine whether the NLR or the PLR would predict the clinical outcomes in advanced gastric cancer patients treated with oxaliplatin/ 5-fluorouracil (FOLFOX). METHODS: The study population consisted of 174 advanced gastric cancer patients. Patients were treated with 85 mg/m² of oxaliplatin as a 2-h infusion at day 1 plus 20 mg/m² of leucovorin over 10 min, followed by 5-FU bolus 400 mg/m² and 22-h continuous infusion of 600 mg/m² at days 1-2. Treatment was repeated in 2-week intervals. The NLR and PLR were calculated from complete blood counts in laboratory test before and after first cycle of chemotherapy. RESULTS: NLR was a useful prognostic biomarker for predicting inferior overall survival (OS) ($p = 0.005$), but was not associated with progression free survival (PFS) ($p = 0.461$). The normalization of NLR after one cycle of chemotherapy was found to be in association with significant improvement in PFS (5.3 months vs. 2.4 months, $p < 0.001$), and OS (11.9 months vs. 4.6 months, $p < 0.001$). The normalization of PLR was also associated with longer PFS (5.6 months vs. 3.4 months, $p = 0.006$), and OS (16.9 months vs. 10.9 months, $p = 0.002$). In multivariate analysis, changes in NLR were associated with PFS (Hazard ratio (HR): 2.297, 95% confidence interval (CI): 1.429-3.693, $p = 0.001$). The NLR, (HR: 0.245, 95% CI: 0.092-0.633, $p = 0.004$), PLR (HR: 0.347, 95% CI: 0.142-0.847, $p = 0.020$), changes in NLR (HR: 2.468, 95% CI: 1.567-3.886, $p < 0.001$), and changes in PLR (HR: 1.473, 95% CI: 1.038-2.090, $p = 0.030$) were independent prognostic markers for OS. CONCLUSION: This study demonstrates that NLR, PLR, and changes in NLR or PLR are independent prognostic factor for OS in patients with advanced gastric cancer treated with chemotherapy. These specific factors may also help in identifying the patients, who are more sensitive to FOLFOX regimen.

[806]

TÍTULO / TITLE: - Evaluation of clinical value of single nucleotide polymorphisms of dihydropyrimidine dehydrogenase gene to predict 5-Fluorouracil toxicity in 60 colorectal cancer patients in china.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Med Sci. 2013 May 20;10(7):894-902. doi: 10.7150/ijms.5556. Print 2013.

●● Enlace al texto completo (gratis o de pago) [7150/ijms.5556](#)

AUTORES / AUTHORS: - Zhang X; Sun B; Lu Z

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, China-Japan Union Hospital, Jilin University, Changchun, China, 130041.

RESUMEN / SUMMARY: - Dihydropyrimidine dehydrogenase (DPD) activity could be affected by single nucleotide polymorphisms (SNPs), resulting in either no effect, partial or complete loss of DPD activity. To evaluate if SNPs of DPD can be used to predict 5-FU toxicity, we evaluated five SNPs of DPD (14G1A, G1156T, G2194A, T85C and T464A) by TaqMan real time PCR in 60 colorectal cancer patients. Clinical data demonstrated that there was higher correlation between DPD activity and toxic effects of 5-FU ($p < 0.05$). Six patients were positive for G2194A detection, which were all heterozygous. Two patients had lower DPD activities (< 3) with higher toxic effects (\geq stage III) while one patient was also positive for T85C detection. Ten patients were positive for T85C detection. Two patients were homozygous with lower DPD activities and higher toxic effects. Two patients were positive for the T464A detection, which were heterozygous with lower DPD activity and higher toxic effects and also positive for T85C detection. These data clearly indicated that the T464A and homozygous of the T85C are stronger biomarkers to predict the 5-FU toxicity. Our study significantly indicated that the detection for G2194A, T85C and T464A could predict ~13% of 5-FU severe toxic side effects.

[807]

TÍTULO / TITLE: - Effective azacitidine treatment for myelodysplastic syndrome transformed from essential thrombocythemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Rinsho Ketsueki. 2013 May;54(5):468-72.

AUTORES / AUTHORS: - Iizuka H; Yoshimi A; Yamamoto G; Masuda A; Nannya Y; Ichikawa M; Yatomi Y; Kurokawa M

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, The University of Tokyo Hospital.

RESUMEN / SUMMARY: - A 68-year-old woman with essential thrombocythemia had been treated with hydroxycarbamide and aspirin for 13 years. She exhibited the rapid progression of anemia, and a bone marrow examination showed dysplasia of the erythroid cells, myeloid cells, and megakaryocytes. Karyotype analysis indicated complex abnormalities including der (5;21)(p10;q10). She was diagnosed with myelodysplastic syndrome (MDS), refractory anemia with excess blasts-1 (RAEB-1). Lenalidomide was started, but no improvement in

anemia was recorded. Lenalidomide was discontinued due to eosinophilia, basophilia, and a skin rash. Azacitidine was administered. The patient became transfusion independent, and a complete cytogenetic response was achieved with three courses of azacitidine. However, disease progression to acute myeloid leukemia (AML) was observed after an additional two courses of azacitidine, which was resistant to induction chemotherapy. The patient died five months later from AML transformation. Azacitidine may be effective in MDS transformed from essential thrombocythemia, and also in lenalidomide-resistant MDS with the deletion of 5q.

[808]

TÍTULO / TITLE: - Tumor Site- and Stage-Specific Associations between Allelic Variants of Glutathione S-Transferase and DNA-Repair Genes and Overall Survival in Colorectal Cancer Patients Receiving 5-Fluorouracil-Based Chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e69039. doi: 10.1371/journal.pone.0069039. Print 2013.

- Enlace al texto completo (gratis o de pago)

1371/journal.pone.0069039

AUTORES / AUTHORS: - Lai CY; Hsieh LL; Sung FC; Tang R; Bai CH; Wu FY; Chiou HY; Yeh CC

INSTITUCIÓN / INSTITUTION: - Department of Public Health, College of Public Health, China Medical University, Taichung City, Taiwan.

RESUMEN / SUMMARY: - INTRODUCTION: Our retrospective cohort study investigated the effect of tumor site and stage on the associations between the allelic variants of glutathione S-transferase (GST) and DNA-repair genes and overall survival (OS) in CRC patients treated with 5-fluorouracil (5-FU)-based adjuvant chemotherapy. MATERIAL AND METHODS: We genotyped GSTM1, GSTT1, GSTP1 Ile105Val, XRCC1 Arg399Gln, XRCC3 Thr241Met, and XPD Lys751Gln in 491 CRC patients between 1995 and 2001. A Cox proportional-hazards model was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationships between the allelic variants and OS. Survival analyses were performed for each allelic variant by using the log-rank test and Kaplan-Meier analysis. RESULTS: The CRC patients with the XPD Gln allelic variants had poorer survival than patients with the Lys/Lys genotype (HR = 1.38, 95% CI = 1.02-1.87), and rectal cancer patients had the poorest survival among them (HR = 1.87, 95% CI = 1.18-2.95). A significantly shorter OS was observed among stage II/III colon cancer patients with the XRCC1 Gln allelic variants (HR = 1.69, 95% CI = 1.06-2.71), compared to those with XRCC1 Arg/Arg genotype. In the combined analysis of the XRCC1 and XPD genes patients with stage II/III tumors, the poorest OS occurred in colon cancer patients with the XRCC1 Gln and XPD Gln allelic variants (HR =

2.60, 95% CI = 1.19-5.71) and rectal cancer patients with the XRCC1 Arg/Arg and XPD Gln allelic variants (HR = 2.77, 95% CI = 1.25-6.17). CONCLUSION: The XPD and XRCC1 allelic variants may be prognostic markers for CRC patients receiving 5-FU based chemotherapy. The contributions of the XPD and XRCC1 allelic variants to OS are tumor site- and/or stage-dependent.

[809]

TÍTULO / TITLE: - Recurrent Gastrointestinal Hemorrhage in Treatment with Dasatinib in a Patient Showing SMAD4 Mutation with Acute Lymphoblastic Leukemia Philadelphia Positive and Juvenile Polyposis Hereditary Hemorrhagic Telangiectasia Syndrome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hematol Rep. 2013 Jul 3;5(2):26-7. doi: 10.4081/hr.2013.e7. Print 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [4081/hr.2013.e7](#)

AUTORES / AUTHORS: - Sartor C; Papayannidis C; Chiara Abbenante M; Iacobucci I; Broccoli A; Venturi C; Testoni N; Ferrari A; Martinelli G

INSTITUCIÓN / INSTITUTION: - Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy.

RESUMEN / SUMMARY: - We report a case of a patient affected by juvenile polyposis and hereditary hemorrhagic telangiectasia linked to a SMAD4 mutation who developed acute lymphoblastic leukemia positive for the Philadelphia chromosome translocation and with a complex karyotype. During the treatment with the tyrosine kinase inhibitor dasatinib the patient presented recurrent severe gastrointestinal hemorrhages linked to the genetic background and aggravated by thrombocytopenia.

[810]

TÍTULO / TITLE: - Change of influence of prognostic markers on metastasis free interval during and after adjuvant tamoxifen therapy in breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J BUON. 2013 Apr-Jun;18(2):321-7.

AUTORES / AUTHORS: - Abu Rabi Z; Todorovic-Rakovic N; Markicevic M; Stamatovic L; Vujasinovic T; Nikolic-Vukosavljevic D

INSTITUCIÓN / INSTITUTION: - Laboratory for Receptors and Biology of Malignant Tumors, Division of Experimental Oncology, Institute of Oncology and Radiology of Serbia, Belgrade, Serbia.

RESUMEN / SUMMARY: - Purpose: To evaluate the influence of molecular biomarkers (estrogen receptor - ER, progesterone receptor - PR, and human epidermal growth factor receptor2 - HER2) and pathological parameters on metastasis free interval (MFI) in adjuvantly tamoxifen-treated breast cancer patients, during different follow up periods (0-2.5 years, 2.5-5 years and 5-12 years). Methods: The study included 113 postmenopausal breast cancer patients with known pathological parameters. Steroid receptors were

determined by ligand-binding assay and HER2 amplification status by chromogenic in situ hybridization (CISH). Results: During the first 2.5 years of therapy patients with ER <5 fmol/mg, PR <5 fmol/mg or pT2 (>=2cm) tumors had higher probability of distant metastasis. For the period between 2.5-5 years, analysis of MFI according to pathological parameters and molecular biomarkers, separately, did not show any statistically significant difference. Patients with pT>=2 cm and HER2 amplification had much greater chance of developing distant metastasis when compared to other phenotypes (HER2-negative/pT1, HER2-negative/pT2 and HER2-positive/pT1). Patients with ER >=160 fmol/mg and PR >=45 fmol/mg had good prognosis after 5 years of tamoxifen therapy. Conclusion: Our study indicates that there is a change of influence of the analyzed pathological parameters on MFI, depending on different follow up periods. Steroid receptor status, tumor size and HER2 status (alone or in combination) are significant parameters for the course of disease of postmenopausal ER-positive breast cancer patients, but during different periods of follow up.

[811]

TÍTULO / TITLE: - Subcutaneous Omacetaxine Mepesuccinate in Patients With Chronic-Phase Chronic Myeloid Leukemia Previously Treated With 2 or More Tyrosine Kinase Inhibitors Including Imatinib.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Jun 17. pii: S2152-2650(13)00122-5. doi: 10.1016/j.clml.2013.03.020.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.03.020

AUTORES / AUTHORS: - Cortes JE; Nicolini FE; Wetzler M; Lipton JH; Akard L; Craig A; Nanda N; Benichou AC; Leonoudakis J; Khoury HJ; Hochhaus A; Baccarani M; Kantarjian HM

INSTITUCIÓN / INSTITUTION: - The University of Texas MD Anderson Cancer Center, Houston, TX. Electronic address: jcortes@mdanderson.org.

RESUMEN / SUMMARY: - INTRODUCTION: Omacetaxine mepesuccinate (omacetaxine) is a first-in-class cephalotaxine that has demonstrated efficacy in CML. In this analysis we evaluated omacetaxine in CML patients with resistance or intolerance to 2 or more tyrosine kinase inhibitors (TKIs). PATIENTS AND METHODS: Data were pooled from 2 phase II trials of subcutaneous omacetaxine, administered at 1.25 mg/m² twice daily for 14 consecutive days every 28 days until response, then for 7 days every 28 days as maintenance. Patients with resistance or intolerance to imatinib and at least 1 other approved TKI (dasatinib and/or nilotinib) were included; results for patients in chronic phase (CP) are reported here. Major cytogenetic response (MCyR) was the primary end point. RESULTS: Eighty-one patients with CML-CP (median age, 59 years; range, 26-83 years) were included in the analysis. All patients previously received imatinib, 69 (85%) previously received dasatinib, and 48 (59%) previously received nilotinib. Median omacetaxine

exposure was 7.5 months (range, 0.03-38.6 months), with 13 patients ongoing. MCyR was reported in 16 patients (20%; one-sided 95% lower confidence limit, 12.8%), including 8 complete responses; median duration was 17.7 months (95% confidence interval, 4.1 months - not reached). Fifty-six patients (69%) achieved and/or maintained hematologic response for at least 8 weeks; median duration was 12.2 months (range, 8.4-26.2 months). Median failure-free and overall survival were 9.6 months and 34 months, respectively. Toxicity was mainly hematologic: the most common grade \geq 4 adverse events were thrombocytopenia (67%), neutropenia (47%), and anemia (37%).
CONCLUSION: Omacetaxine produced clinically meaningful responses with acceptable tolerability in patients with CML-CP previously treated with 2 or more TKIs.

[812]

TÍTULO / TITLE: - Development of a novel interferon-alpha2b gene construct with a repetitive hypoxia-inducible factor binding site and its suppressive effects on human renal cell carcinoma cell lines in vitro.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Clin Oncol. 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1007/s10147-013-0568-](#)

[Z](#)

AUTORES / AUTHORS: - Fukui N; Kageyama Y; Higashi Y; Kihara K; Kizaka-Kondoh S; Hiraoka M; Shinojima T; Suzuki K; Oya M

INSTITUCIÓN / INSTITUTION: - Department of Urology, Saitama Cancer Center, 818 Komuro, Ina, Kita-Adachi-gun, Saitama, 362-0806, Japan, [na-](mailto:na-fukui@cancer-c.pref.saitama.jp)

fukui@cancer-c.pref.saitama.jp.

RESUMEN / SUMMARY: - BACKGROUND: Despite the advent of targeted therapies, interferon-alpha (IFN-alpha) remains a therapeutic option for advanced renal cell carcinoma (RCC), especially in Japan, with a treatment response rate of 15-20 %. To improve the efficacy of IFN-alpha-based therapies, we evaluated a novel treatment strategy for RCC using an IFN-alpha2b gene construct with a repetitive hypoxia-inducible factor binding site. METHODS: We constructed an expression plasmid designated 5HREp-IFN-alpha2b containing the coding region of the IFN-alpha2b gene. Five copies of the hypoxia-response element (HRE) sequences were inserted upstream of the IFN-alpha2b gene, and the construct was transfected into human RCC cell lines ACHN, 786-O and KU19-20. The concentrations of IFN-alpha2b in the conditioned media were measured by enzyme-linked immunosorbent assay. Cell viabilities were determined by MTS assays. RESULTS: Construct-induced IFN-alpha secretion was confirmed in all three cell lines. IFN-alpha production was significantly enhanced by the hypoxia-mimicking agent deferoxamine mesylate in cell lines expressing the wild-type von Hippel-Lindau (VHL) gene (KU19-20 and ACHN) compared with cells expressing the mutant VHL gene (786-O). The construct exerted significant suppressive effects on the viabilities

of all RCC cell lines. CONCLUSION: This is the first study to report on the construction of a cytokine gene with a repetitive hypoxia-inducible factor binding site and its application in the suppression of human cancer cells. Gene therapy using this IFN- α 2b gene construct with HREs may represent a novel treatment modality for advanced RCC.

[813]

TÍTULO / TITLE: - Value of carbohydrate antigen 19-9 in predicting response and therapy control in patients with metastatic pancreatic cancer undergoing first-line therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Oncol. 2013 Jun 14;3:155. doi: 10.3389/fonc.2013.00155. Print 2013.

●● Enlace al texto completo (gratis o de pago) [3389/fonc.2013.00155](#)

AUTORES / AUTHORS: - Pelzer U; Hilbig A; Sinn M; Stieler J; Bahra M; Dorken B; Riess H

INSTITUCIÓN / INSTITUTION: - Department of Hematology/Oncology, Comprehensive Cancer Center, Universitätsmedizin Berlin - Charité, Berlin, Germany.

RESUMEN / SUMMARY: - Background: Serum carbohydrate antigen 19-9 (CA 19-9) has been shown to be a sensitive and specific serum marker for pancreatic cancer. Little has been published about correlations between baseline CA 19-9 level or changes to CA 19-9 level and median overall survival (mOS). Its impact on monitoring treatment efficacy remains under discussion, however. Methods: CA 19-9 serum level was measured in 181 consecutive patients with advanced pancreatic cancer (APC) being treated with gemcitabine-based first-line chemotherapy. We separated the patients into several groups depending on baseline CA 19-9 levels and the CA 19-9 response after 6-8 weeks of treatment. Evaluations were made using SPSS 19.9. Results: Median baseline CA 19-9 level was 1,493 U/ml (range 40-1,043,301). Patients with baseline CA 19-9 \leq 1,000 U/ml had a mOS of 14.9 months (95% CI: 11.36:18.44), whereas patients with CA 19-9 $>$ 1,000 U/ml had a mOS of 7.4 months [(95% CI: 5.93:8.87) $p < 0.001$, HR 2.12]. With regard to the change in CA 19-9 after 6-8 weeks of treatment: patients with increased CA 19-9 levels had a mOS of 8.1 months, those with stabilized CA 19-9 levels 11.6 months, and those with decreased CA 19-9 levels 11.1 months ($p < 0.019$). Conclusion: CA 19-9 levels can separate patients with differing mortality risks at baseline. Patients with stabilization or high response of CA 19-9 after 6-8 weeks of treatment had no significant differences in survival rates, whereas patients with increased CA 19-9 had significantly lower survival rates, indicating an early treatment failure.

[814]

TÍTULO / TITLE: - Effect of Jinlong capsule on proliferation and apoptosis of human pancreatic cancer cells BxPC-3.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Tradit Chin Med. 2013 Apr;33(2):205-10.

AUTORES / AUTHORS: - Li Y; Hu J; Huang H; He Y

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Guang'an men Hospital Affiliated to China Academy of Chinese Medical Sciences, Beijing 100053, China.

RESUMEN / SUMMARY: - OBJECTIVE: To study the possible roles of Jinlong capsule (JLC) on the proliferation and apoptosis of human pancreatic cancer cells BxPC-3. METHODS: The human pancreatic cancer cells BxPC-3 were treated with JLC at the concentration of 0.05-1.00 mg/mL for 24-120 h. The inhibition rate of JLC on human pancreatic cancer cells BxPC-3 was detected by 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. Flow cytometry was employed to measure cell apoptosis using Annexin V-FITC/Propidium iodide (AV-FITC/PI) method. Cell cycles were determined by PI staining. The expression of 5100 Calcium binding protein A4 (S100A4) in cell matrix was measured by enzyme-linked immunosorbent assay (ELISA). The expression levels of apoptosis-related protein such as BCL2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), B-cell lymphoma/leukemia-2 (Bcl-2) and Cysteinylnaspartate specific proteinase 3 (Caspase-3) were detected by Western blotting. RESULTS: JLC significantly inhibited the proliferation of human pancreatic cancer cells BxPC-3 in a dose-dependent and time-dependent manner. JLC promoted cell apoptosis and maintained cell cycle in S and G2/M phase rather than G1/G0 phase. The expression of S100A4 in the cell matrix was reduced. The expression of cell apoptotic protein BNIP3 was increased while Bcl-2 was decreased. CONCLUSION: JLC can inhibit the proliferation of human pancreatic cancer cells BxPC-3 by stimulating cell apoptosis, arresting the cell cycle at S and G2/M phase which blocks the circulation of normal cell cycle and reducing the expression of S100A4 protein. Higher pro-apoptosis protein BNIP3 and lower anti-apoptosis protein Bcl-2 levels were found, which may be related to the apoptotic effects of JLC.

[815]

TÍTULO / TITLE: - High-Dose Interleukin-2 (HD IL-2) Therapy Should Be Considered for Treatment of Patients with Melanoma Brain Metastases.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chemother Res Pract. 2013;2013:726925. doi: 10.1155/2013/726925. Epub 2013 May 13.

●● Enlace al texto completo (gratis o de pago) [1155/2013/726925](#)

AUTORES / AUTHORS: - Chu MB; Fesler MJ; Armbrecht ES; Fosko SW; Hsueh E; Richart JM

INSTITUCIÓN / INSTITUTION: - Department of Dermatology, Anheuser-Busch Institute, Saint Louis University, 1402 S. Grand Boulevard., 4th Floor, St. Louis, MO 63104, USA.

RESUMEN / SUMMARY: - A retrospective review was performed on patients with stable melanoma brain metastases treated with HD IL-2 therapy (720,000 IU/kg per dose intravenously; 14 doses, 2 cycles per course, maximum 2 courses) from January 1999 to June 2011 at Saint Louis University. There were 5 men and 3 women; median age was 52.2 years (26.8-61.1 years). One patient started treatment with lung lesions only (after resection of melanoma brain disease) and experienced partial response. Seven patients had brain metastases at treatment initiation. Median overall survival (mOS) for entire cohort (n = 8) was 8.7 months (2.1 to 19.0 months). All patients with brain metastases at first dose (n = 7) showed progressive disease; mOS was 6.7 months (range 2.1-18.2 months) for this group. Patients received radiosurgery and whole brain radiation before and after HD IL-2 therapy. One patient had symptoms suggestive of neurotoxicity. A history of alcohol abuse was revealed during admission. The patient's symptoms improved with initiation of an alcohol withdrawal protocol. In this analysis, patients with melanoma brain metastases received HD IL-2 without treatment-related mortality. We think that HD IL-2 should be considered as a treatment option in patients with melanoma brain metastases who are otherwise eligible for therapy.

[816]

TÍTULO / TITLE: - Association of multiple drug resistance-1 gene polymorphism with multiple drug resistance in breast cancer patients from an ethnic Saudi Arabian population.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Epidemiol. 2013 May 28. pii: S1877-7821(13)00071-4. doi: 10.1016/j.canep.2013.04.011.

●● Enlace al texto completo (gratis o de pago)

1016/j.canep.2013.04.011

AUTORES / AUTHORS: - Alsaif AA; Hasan TN; Shafi G; Syed NA; Alsaif MA; Al-Assaf AH; Alshatwi AA

INSTITUCIÓN / INSTITUTION: - Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

RESUMEN / SUMMARY: - Chemotherapy has been used widely to treat cancer, both as a systemic therapy and as a local treatment. Unfortunately, many types of cancer are still refractory to chemotherapy. The mechanisms of anticancer drug resistance have been extensively explored but have not been fully characterized. This study analyzed the occurrences of polymorphism (SNP) in the MDR1 gene in breast cancer patients and determined a possible association with chemotherapy. The study group included one hundred breast carcinoma patients who subsequently received chemotherapy (the regimen generally consisted of commonly used drugs such as cyclophosphamide,

adriamycin, 5-fluorouracil, docetaxel and their combinations). Blood samples from 100 healthy individuals are used, as controls were also genotyped for the MDR1 gene. This investigation revealed a significant correlation with response to various regimens of chemotherapy showing a low response to therapy with the CT/TT genotype at (exon 12) 1236 codon ($p < 0.001$). These findings demonstrate, for the first time, that the polymorphisms in (exon 12) 1236 codon of the MDR1 gene greatly influence the drug response in patients from the Arab population of Saudi Arabia.

[817]

TÍTULO / TITLE: - Prognostic Factors for Metastatic Urothelial Carcinoma Undergoing Cisplatin-based Salvage Chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Jpn J Clin Oncol. 2013 Jul 25.

●● Enlace al texto completo (gratis o de pago) [1093/jjco/hyt096](#)

AUTORES / AUTHORS: - Taguchi S; Nakagawa T; Hattori M; Niimi A; Nagata M; Kawai T; Fukuhara H; Nishimatsu H; Ishikawa A; Kume H; Homma Y

INSTITUCIÓN / INSTITUTION: - Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

RESUMEN / SUMMARY: - **OBJECTIVE:** To assess the clinicopathologic factors influencing survival in patients with metastatic urothelial carcinoma undergoing salvage chemotherapy. **METHODS:** A retrospective review was conducted on cases of metastatic urothelial carcinoma who underwent cisplatin-based salvage chemotherapy at our institution between April 2003 and July 2011. The association of various clinicopathologic factors with survival was assessed. Survival curves were constructed by the Kaplan-Meier method. A log-rank test for univariate analysis and a Cox proportional hazards model for multivariate analysis were used. **RESULTS:** Eighty-three cases were identified in the study. Among them, 64 patients were dead during the follow-up. The median survival was 14.6 months. Multivariate analysis evaluating variables at the start of chemotherapy demonstrated that liver metastasis, performance status score ≥ 2 and leukocyte counts $\geq 8000/\mu\text{mol}$ were significant predictive factors for poor outcome. Based on these three pre-induction variables, a risk model predicting the overall survival from the initiation of chemotherapy was constructed, which classified patients into three groups with significantly different overall survival ($P < 0.0001$). Additionally, factors after induction of chemotherapy were studied, and poor response for chemotherapy and absence of focal treatment for metastatic lesions were also significantly associated with poorer survival. **CONCLUSIONS:** Liver metastasis, poor performance status and higher leukocyte counts were independent poor prognostic indicators for metastatic urothelial carcinoma. Our risk classification enables an accurate prediction of survival that can be useful in deciding which patients are likely to benefit from salvage chemotherapy.

[818]

TÍTULO / TITLE: - Impact of genetic polymorphisms on adenoma recurrence and toxicity in a COX2 inhibitor (celecoxib) trial: results from a pilot study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharmacogenet Genomics. 2013 Aug;23(8):428-437.

- Enlace al texto completo (gratis o de pago)

[1097/FPC.0b013e3283631784](#)

AUTORES / AUTHORS: - Kraus S; Hummler S; Toriola AT; Poole EM; Scherer D; Kotzmann J; Makar KW; Kazanov D; Galazan L; Naumov I; Coghill AE; Duggan D; Gigic B; Arber N; Ulrich CM

INSTITUCIÓN / INSTITUTION: - aIntegrated Cancer Prevention Center, Tel Aviv Sourasky Medical Center bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel cNational Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), Heidelberg, Germany dDepartment of Surgery, Division of Public Health Sciences, Siteman Cancer Center, Washington University School of Medicine, St Louis, Missouri eFred Hutchinson Cancer Research Center, Seattle, Washington fDepartment of Medicine, Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School gDepartment of Epidemiology, Harvard School of Public Health, Boston, Massachusetts hTranslational Genomics Research Institute, Phoenix, Arizona, USA.

RESUMEN / SUMMARY: - **OBJECTIVE:** Chemoprevention trials have shown that celecoxib reduces adenoma recurrence but can cause cardiovascular toxicity. In this pilot study, we evaluated associations between genetic variation in several candidate pathways (e.g. prostaglandin synthesis) and adenoma recurrence and cardiovascular and gastrointestinal toxicities. **METHODS:** Genotyping analysis was carried out on 117 Israeli colorectal adenoma patients who participated in the Prevention of Colorectal Sporadic Adenomatous Polyps trial. Reassessment followed after 3 years on celecoxib and after 2 years from termination of treatment with celecoxib. Efficacy (absence of colorectal adenomas) was measured by colonoscopy at years 1, 3, and 5. Toxicities were assessed by investigators during celecoxib treatment and by self-report post-treatment. A linkage disequilibrium-based selection algorithm ($r \geq 0.90$, $MAF \geq 4\%$) identified 255 tagSNPs in 25 analyzed candidate genes. Genotyping was performed by using Illumina GoldenGate technology. **RESULTS:** Multiple genetic variants were associated with adenoma recurrence and toxicity. Genetic variability in COX1, COX2, and ALOX12/15 genes played a role in adenoma recurrence, particularly among patients on placebo. More gene variants (especially variants in PGES, CRP, SRC, and GPX3) were associated with increased risk for cardiovascular toxicity and symptoms, compared with gastrointestinal toxicity and symptoms. The increased risk for cardiovascular toxicity/symptoms associated with the SRC gene variants (rs6017996, rs6018256, rs6018257) ranged from 6.61 (95% confidence interval

1.66-26.36, $P < 0.01$) to 10.71 (95% confidence interval 1.96-58.60, $P < 0.01$).
CONCLUSION: Genetic polymorphisms in multiple inflammation-related genes appear to interact with celecoxib on adenoma recurrence and its attendant toxicity, particularly cardiovascular toxicity/symptoms. Larger studies validating these pharmacogenetic relationships are needed.

[819]

TÍTULO / TITLE: - Retrospective Analysis of Prognostic Factors Associated With Response and Overall Survival by Baseline Marrow Blast Percentage in Patients With Myelodysplastic Syndromes Treated With Decitabine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Jun 19. pii: S2152-2650(13)00154-7. doi: 10.1016/j.clml.2013.05.004.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.05.004

AUTORES / AUTHORS: - Jabbour E; Kantarjian H; O'Brien S; Kadia T; Malik A; Welch MA; Teng A; Cortes J; Ravandi F; Garcia-Manero G

INSTITUCIÓN / INSTITUTION: - The University of Texas MD Anderson Cancer Center, Houston, TX. Electronic address: ejabbour@mdanderson.org.

RESUMEN / SUMMARY: - BACKGROUND: After the World Health Organization (WHO) changed the definition of acute myeloid leukemia (AML) to $\geq 20\%$ blasts, the International Working Group (IWG) response criteria for myelodysplasia were updated. This retrospective analysis evaluated response to decitabine using updated IWG criteria in patients pooled from 2 decitabine trials. PATIENTS AND METHODS: Outcomes for patients with myelodysplastic syndrome (MDS) with baseline marrow blasts $\geq 20\%$ and $< 30\%$ (RAEB-t group) and $< 20\%$ (MDS group) were compared. RESULTS: Patients with RAEB-t ($n = 26$) had a significantly shorter time from diagnosis to study treatment (7.3 vs. 18.3 months), a higher International Prognostic Scoring System (IPSS) risk (77% vs. 16% high-risk patients), and lower median baseline platelet count (62.3 vs. 112.7 $\times 10^3/\mu\text{L}$) vs. patients with MDS ($n = 157$), yet no significant difference in overall response rate (ORR) (15.4% vs. 28.0%). Patients with MDS had better duration of response (9.9 vs. 5 months; $P = .024$) and overall survival (OS) (16.6 vs. 9.0 months; $P = .021$) compared with patients with RAEB-t. CONCLUSION: Decitabine is active in and may benefit patients with $> 20\%$ blasts (RAEB-t).

[820]

TÍTULO / TITLE: - Interferon-based therapy decreases risks of hepatocellular carcinoma and complications of cirrhosis in chronic hepatitis C patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e70458. doi: 10.1371/journal.pone.0070458. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0070458

AUTORES / AUTHORS: - Hsu CS; Huang CJ; Kao JH; Lin HH; Chao YC; Fan YC; Tsai PS

INSTITUCIÓN / INSTITUTION: - Division of Gastroenterology, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Taipei Branch, Taipei, Taiwan ; School of Medicine, Tzu Chi University, Hualien, Taiwan.

RESUMEN / SUMMARY: - **BACKGROUND:** Interferon-based therapy (IBT) has been the standard of care for hepatitis C virus (HCV) infection. However, conflicting results exist regarding the effects of IBT on risk of developing hepatocellular carcinoma (HCC) and cirrhosis-associated complications, and most included highly selected patients. **METHODS:** This 8-year cohort study was based on the Longitudinal Health Insurance Database 2000 (LHID 2000) consisting of 1,000,000 beneficiaries randomly selected from all Taiwan National Health Insurance enrollees in 2000 (>23.7 million). Patients with newly detected HCV infections (n = 11,264) were classified based on treatment and clinical outcomes. IBTs were defined as regimens that included interferon- alfa, pegylated interferon- alfa -2^a, or pegylated interferon- alfa -2b for at least 3 months. The Cox proportional hazards models were used to estimate the hazard ratio (HR) and associated confidence interval (CI) of HCC and cirrhosis-associated complications for IBT. **RESULTS:** The 8-year incidence rate for HCC was 3.9% among patients who received IBT and 5.6% among those who did not. The HCC-free survival rate was significantly higher among patients receiving IBT during the 8-year period than their counterpart (adjusted HR, 0.50; 95% CI, 0.31-0.81; P = .004). Similarly, the event-free survival rates for esophageal variceal bleeding (adjusted HR, 0.45; 95% CI, 0.22-0.91; P = .026), hepatic encephalopathy (adjusted HR, 0.38; 95% CI, 0.21-0.69; P = .001), ascites (adjusted HR, 0.28; 95% CI, 0.14-0.57; P<.001), and cirrhosis (adjusted HR, 0.63; 95% CI, 0.44-0.91; P = .013) were significantly higher among patients who received IBT than those who did not, after adjustment for associated factors. **CONCLUSION:** Treatment with interferon may reduce the 8-year risk of HCC and cirrhosis-associated complications in patients with chronic HCV infection.

[821]

TÍTULO / TITLE: - Diagnostic and prognostic value of tumor M2-pyruvate kinase levels in patients with colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Turk J Gastroenterol. 2013 Feb;24(1):36-42.

AUTORES / AUTHORS: - Demir AS; Erdenen F; Muderrisoethlu C; Toros AB; Bektas H; Gelisgen R; Tabak O; Altunoethlu E; Uzun H; Huq GE; Aral H

INSTITUCIÓN / INSTITUTION: - Departments of Internal Medicine, General Surgery, Pathology and Biochemistry, Istanbul Training and Research Hospital, Istanbul.

RESUMEN / SUMMARY: - Background/aims: Screening for precancerous lesions is important for the diagnosis and treatment of colorectal tumors. We

investigated M2-pyruvate kinase levels in patients with colorectal polyps and carcinoma and assessed factors affecting M2-pyruvate kinase levels. Materials and Methods: Eighty-five patients who had undergone colonoscopic examination and who were diagnosed with a neoplastic lesion were included. Patients were divided into two groups according to the macroscopic diagnosis of polyp or carcinoma. According to histopathological evaluation, specimens were grouped as nonneoplastic lesions, tubular adenoma, tubulovillous adenoma and adenocarcinoma. M2-pyruvate kinase levels were measured with the Tumor M2-pyruvate kinase ELISA kit. Results: Mean M2-pyruvate kinase levels were 76.1+/-57.73 (13.1-288.22) IU/ml. We did not find a correlation between M2-pyruvate kinase levels and age, gender, smoking, alcohol and aspirin consumption and colorectal cancer family history. There was a relationship between body mass index and M2-pyruvate kinase level ($p=0.022$). The carcinoma group had the highest levels of M2-pyruvate kinase both endoscopically and histopathologically ($p=0.009$, $p=0.019$ respectively). M2-pyruvate kinase levels of patients who died were significantly higher than patients who survived ($p=0.001$). Enzyme values were significantly lower in diabetic patients than nondiabetics ($p=0.04$); and chronic renal failure patients had higher levels ($p=0.045$). Conclusion: Serum M2-pyruvate kinase levels may be useful in distinguishing malignant and benign lesions of the colon and may provide insight in terms of survival.

[822]

TÍTULO / TITLE: - Pretreatment long interspersed element (LINE)-1 methylation levels, not early hypomethylation under treatment, predict hematological response to azacitidine in elderly patients with acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jun 20;6:741-8. doi: 10.2147/OTT.S45459. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S45459](#)

AUTORES / AUTHORS: - Cross M; Bach E; Tran T; Krahl R; Jaekel N; Niederwieser D; Junghanss C; Maschmeyer G; Al-Ali HK

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, University of Leipzig, Leipzig, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Epigenetic modulations, including changes in DNA cytosine methylation, are implicated in the pathogenesis and progression of acute myeloid leukemia (AML). Azacitidine is a hypomethylating agent that is incorporated into RNA as well as DNA. Thus, there is a rationale to its use in patients with AML. We determined whether baseline and/or early changes in the methylation of long interspersed element (LINE)-1 or CDH13 correlate with bone marrow blast clearance, hematological response, or survival in patients with AML treated with azacitidine. METHODS: An open label, phase I/II trial was performed in 40 AML patients (median bone marrow blast count

was 42%) unfit for intensive chemotherapy treated with azacitidine 75 mg/m²/day subcutaneously for 5 days every 4 weeks. Bone marrow mononuclear cell samples were taken on day 0 (pretreatment) and day 15 during the first treatment cycle; LINE-1 and CDH13 methylation levels were quantified by methylation-specific, semiquantitative, real-time polymerase chain reaction. RESULTS: Treatment with azacitidine significantly reduced LINE-1 but not CDH13 methylation levels over the first cycle (P < 0.0001). Absolute LINE-1 methylation levels tended to be lower on day 0 (P = 0.06) and day 15 of cycle 1 (P = 0.03) in patients who went on to achieve subsequent complete remission, partial remission or hematological improvement versus patients with stable disease. However, the decrease in LINE-1 methylation over the first treatment cycle did not correlate with subsequent response (P = 0.31). Baseline methylation levels of LINE-1 or CDH13 did not correlate with disease-related prognostic factors, including cytogenetic risk, relapsed/refractory AML, or presence of NPM1 or FLT3 mutations. No correlation was observed between LINE-1 or CDH13 methylation levels and overall survival. CONCLUSION: Analysis of baseline LINE-1 methylation levels may help identify elderly AML patients who are most likely to respond to azacitidine therapy.

[823]

TÍTULO / TITLE: - PAX3-FOXO1 Induces Up-Regulation of Noxa Sensitizing Alveolar Rhabdomyosarcoma Cells to Apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neoplasia. 2013 Jul;15(7):738-48.

AUTORES / AUTHORS: - Marshall AD; Picchione F; Geltink RI; Grosveld GC

INSTITUCIÓN / INSTITUTION: - Department of Genetics, St Jude Children's Research Hospital, Memphis, TN ; Gene and Stem Cell Therapy, Centenary Institute, University of Sydney, Camperdown, New South Wales, Australia.

RESUMEN / SUMMARY: - Alveolar rhabdomyosarcoma (ARMS) has a much poorer prognosis than the more common embryonal subtype. Most ARMS tumors characteristically possess a specific genomic translocation between the genes of PAX3/7 and FOXO1 (FKHR), which forms fusion proteins possessing the DNA binding domains of PAX3/7 and the more transcriptionally potent transactivation domain of FOXO1. We have shown that the proapoptotic BH3-only family member Noxa is upregulated by the PAX3-FOXO1 fusion transcription factor in a p53-independent manner. The increased expression of Noxa renders PAX3-FOXO1-expressing cells more susceptible to apoptosis induced by a gamma-secretase inhibitor (GSI1, Z-LLNle-CHO), the proteasome inhibitor bortezomib, and BH3 mimetic ABT-737. Apoptosis in response to bortezomib can be overcome by shRNA knockdown of Noxa. In vivo treatment with bortezomib reduced the growth of tumors derived from a PAX3-FOXO1-expressing primary myoblast tumor model and RH41 xenografts. We therefore demonstrate that PAX3-FOXO1 up-regulation of Noxa represents an

unanticipated aspect of ARMS tumor biology that creates a therapeutic window to allow induction of apoptosis in ARMS cells.

[824]

TÍTULO / TITLE: - Imatinib mesylate therapy in patients of chronic myeloid leukemia with Philadelphia chromosome positive: an experience from eastern India.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Indian J Hematol Blood Transfus. 2012 Jun;28(2):82-8. doi: 10.1007/s12288-011-0108-9. Epub 2011 Sep 21.

●● Enlace al texto completo (gratis o de pago) [1007/s12288-011-0108-9](#)

AUTORES / AUTHORS: - Mukhopadhyay A; Dasgupta S; Mukhopadhyay S; Bose CK; Sarkar S; Gharami F; Koner S; Basak J; Roy UK

INSTITUCIÓN / INSTITUTION: - Department of Haemato Oncology, Netaji Subhas Chandra Bose Cancer Research Institute, 16 A Park Lane, Kolkata-16 Kolkata, India.

RESUMEN / SUMMARY: - Imatinib inhibits constitutively active BCR-ABL tyrosine kinase of chronic myeloid leukemia (CML). In a long term study it was found superior to interferon alfa plus cytarabine for newly diagnosed CML in the chronic phase. However, till date there is no major study to evaluate eastern Indian CML patients treated with imatinib mesylate. The aim of our study was to see the efficacy, tolerability, toxicity and safety of imatinib in eastern Indian subset of CML population. The present study enrolled 831 patients with CML out of which 197 were excluded due to various reasons of noncompliance, death and not being fit to receive the drug. The rest, 634 (76% of total enrolled) were selected for the evaluation. In the beginning of the study, 603 patients were in chronic phase, 27 in accelerated phase and 4 patients in blast crisis phase. Among 634 patients, 280 patients (44%) received previously either interferon alpha or hydroxyurea and other 354 patients (56%) were previously untreated. Complete hematological remission and major cytogenetic response were 91 and 67%, respectively after 1 year of treatment. Complete molecular remission was 35% after 1 year of treatment. Sixty-four patients (10.1%) were resistant to imatinib mesylate in 5 years. The disease free and overall survival at 60 months were 72.2 and 76.1% respectively. After 60 months of follow up, continuous treatment of chronic phase CML with imatinib as initial therapy was found to be safe and able to induce durable responses in a high proportion of patients.

[825]

TÍTULO / TITLE: - Cutaneous side effects of combined therapy with sorafenib and pegylated interferon alpha-2b in metastatic melanoma (phase II DeCOG trial).

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Dtsch Dermatol Ges. 2013 Jul 23. doi: 10.1111/ddg.12100.

●● Enlace al texto completo (gratis o de pago) [1111/ddg.12100](https://doi.org/10.1111/ddg.12100)

AUTORES / AUTHORS: - Degen A; Weichenthal M; Ugurel S; Trefzer U; Kilian K; Garbe C; Egberts F; Poppe LM; Hauschild A; Gutzmer R

INSTITUCIÓN / INSTITUTION: - Department of Dermatology and Allergology, Hannover Medical School, Germany.

RESUMEN / SUMMARY: - BACKGROUND AND OBJECTIVES: During a clinical study with combined therapy of sorafenib and pegylated interferon alpha-2b (SoraPeg study) of the German Dermatologic Oncology Group (ADO/DeCOG), multiple and severe cutaneous side effects were observed. This study sought to analyze these cutaneous side effects, particularly because future studies with combinations of interferon alpha and targeted therapies are planned.

PATIENTS AND METHODS: In a multicenter phase-II-DeCOG study (NCT00623402) in 10 dermatology centers, 55 patients with metastatic melanoma received a combination of sorafenib (2 x 400 mg/day orally) and pegylated interferon alpha-2b (3 mug/kg body weight 1 x/week subcutaneously). All cutaneous side effects were documented. **RESULTS:** Forty-one patients (74.5 %) developed cutaneous side effects, particularly exanthems (51.2 %), hand-foot syndrome (36.5 %), alopecia (36.5 %) and pruritus (24.4 %). Due to the cutaneous side effects, dose reductions were required in 10 patients, interruption of therapy in 10 cases and permanent discontinuation of therapy and in one patient with extensive follicular-cystic lesions. Exanthems were seen more frequently in women (76.2 %) than in men (23.8 %). The occurrence of cutaneous side effects was not correlated with clinical outcome or prognosis. **CONCLUSIONS:** The combination of sorafenib/pegylated interferon alpha-2b caused more cutaneous side effects than have been reported for single agents. Despite intensive dermatologic management of the cutaneous side effects 24 % of patients required a dose modification.

[826]

TÍTULO / TITLE: - Prognostic value of organic anion transporting polypeptide 1B3 and copper transporter 1 expression in endometrial cancer patients treated with paclitaxel and carboplatin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res. 2013;34(3):143-51.

AUTORES / AUTHORS: - Ogane N; Yasuda M; Kameda Y; Yokose T; Kato H; Itoh A; Nishino S; Hashimoto Y; Kamoshida S

INSTITUCIÓN / INSTITUTION: - Department of Pathology Kanagawa Cancer Center Hospital, 1-1-2 Nakao, Asahi, Yokohama 241-0815, Japan.

RESUMEN / SUMMARY: - Paclitaxel and carboplatin (TC) chemotherapy is an effective and well-tolerated regimen against advanced endometrial cancer. Organic anion transporting polypeptide 1B3 (OATP1B3) and copper transporter 1 (CTR1) are critical for the uptake of paclitaxel and carboplatin, respectively.

This study aimed to address the prognostic impact of OATP1B3 and CTR1 in endometrial cancer patients treated with adjuvant TC chemotherapy. We immunohistochemically evaluated the expressions of OATP1B3 and CTR1 in 47 stage III endometrial cancers. The high expression levels of OATP1B3 were significantly correlated with type I tumor ($P = 0.0005$). In univariate analysis, high expression levels of OATP1B3 ($P = 0.047$) and CTR1 ($P = 0.009$) were significantly associated with longer disease-free survival (DFS) and longer overall survival (OS), respectively. The patients with tumors showing high expression levels of at least one of OATP1B3 and CTR1 had potentially longer DFS ($P = 0.058$) and significantly longer OS ($P = 0.003$) in the univariate analysis. Combined OATP1B3/CTR1 expression was the sole independent prognostic factor for longer OS in the multivariate analysis ($P = 0.013$). Our findings suggest that combined OATP1B3/CTR1 expression is a possible predictive/prognostic factor for a good outcome in stage III endometrial cancer patients treated with adjuvant TC chemotherapy.

[827]

TÍTULO / TITLE: - The dyslipidemia-associated SNP on the APOA1/C3/A5 gene cluster predicts post-surgery poor outcome in Taiwanese breast cancer patients: a 10-year follow-up study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 5;13:330. doi: 10.1186/1471-2407-13-330.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-330](#)

AUTORES / AUTHORS: - Hsu MC; Lee KT; Hsiao WC; Wu CH; Sun HY; Lin IL; Young KC

INSTITUCIÓN / INSTITUTION: - Research Center for Medical Laboratory Biotechnology, College of Medicine, National Cheng Kung University, Tainan, Taiwan. t7908077@mail.ncku.edu.tw.

RESUMEN / SUMMARY: - BACKGROUND: Post-surgery therapies are given to early-stage breast cancer patients due to the possibility of residual micrometastasis, and optimized by clinicopathological parameters such as tumor stage, and hormone receptor/lymph node status. However, current efficacy of post-surgery therapies is unsatisfactory, and may be varied according to unidentified patient genetic factors. Increases of breast cancer occurrence and recurrence have been associated with dyslipidemia, which can attribute to other known risk factors of breast cancer including obesity, diabetes and metabolic syndrome. Thus we reasoned that dyslipidemia-associated nucleotide polymorphisms (SNPs) on the APOA1/C3/A5 gene cluster may predict breast cancer risk and tumor progression. METHODS: We analyzed the distribution of 5 selected APOA1/C3/A5 SNPs in recruited Taiwanese breast cancer patients ($n=223$) and healthy controls ($n=162$). The association of SNP (APOA1 rs670) showing correlation with breast cancer with baseline and follow-up parameters was further examined. RESULTS: APOA1 rs670 A allele carriage was higher in

breast cancer patients than controls (59.64% vs. 48.77%, $p=0.038$). The rs670 A allele carrying patients showed less favorable baseline phenotype with positive lymph nodes (G/A: OR=3.32, 95% CI=1.77-6.20, $p<0.001$; A/A: OR=2.58, 95% CI=1.05-6.32, $p=0.039$) and negative hormone receptor expression (A/A: OR=4.85, 95%CI=1.83-12.83, $p=0.001$) in comparison to G/G carriers. Moreover, rs670 A/A carrying patients had higher risks in both tumor recurrence (HR=3.12, 95% CI=1.29-7.56, $p=0.012$) and mortality (HR=4.36, 95% CI=1.52-12.47, $p=0.006$) than patients with no A alleles after adjustments for associated baseline parameters. Furthermore, the prognostic effect of rs670 A/A carriage was most evident in lymph node-negative patients, conferring to the highest risks of recurrence (HR=4.98, 95% CI=1.40-17.70, $p=0.013$) and mortality (HR=9.87, 95%CI=1.60-60.81, $p=0.014$) than patients with no A alleles. CONCLUSIONS: APOA1 rs670 A/A carriage showed poor post-surgery prognosis in Taiwanese lymph node-negative breast cancer patients, whose prognosis were considered better and adjuvant treatment might be less stringent according to currently available assessment protocols. Our findings suggest that APOA1 rs670 indicate a post-surgery risk of breast cancer disease progression, and that carriers of this SNP may benefit from more advanced disease monitoring and therapy regimens than the current regular standards. Furthermore, control of lipid homeostasis might protect APOA1 rs670 minor allele carriers from breast cancer occurrence and progression.

[828]

TÍTULO / TITLE: - Prognostic biomarkers for patients with advanced renal cell carcinoma treated with VEGF-targeted tyrosine kinase inhibitors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jun 13;6:679-84. doi: 10.2147/OTT.S45872. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S45872](#)

AUTORES / AUTHORS: - Cho DC

INSTITUCIÓN / INSTITUTION: - Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA.

RESUMEN / SUMMARY: - Tyrosine kinase inhibitors with activity against vascular endothelial growth factor receptor 2 are now standard treatment for the majority of patients with advanced renal cell carcinoma. The clinical development of these agents followed by their broad clinical utilization has allowed the creation of large databases to facilitate the identification of prognostic biomarkers and development of prognostic models. While several clinical prognostic models have been created, work continues on identifying novel biomarkers which might be used in conjunction with or even in place of these clinical models. In this review, we discuss the progress thus far in improving on current prognostic models and speculate on possible developments in the near future.

[829]

TÍTULO / TITLE: - Prediction of sustained virologic responses to combination therapy of pegylated interferon-alpha and ribavirin in patients with chronic hepatitis C infection.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Family Community Med. 2013 Jan;20(1):35-40. doi: 10.4103/2230-8229.108182.

●● Enlace al texto completo (gratis o de pago) [4103/2230-8229.108182](#)

AUTORES / AUTHORS: - Ismail MH

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Division of Gastroenterology, University of Dammam, College of Medicine, King Fahd Hospital of the University, Al-Khobar, Saudi Arabia.

RESUMEN / SUMMARY: - BACKGROUND AND AIM: Hepatitis C virus (HCV) infection is a major health problem worldwide. Genotype-4 is the most common genotype in Saudi Arabia. The response to treatment with pegylated interferon-alpha combined with ribavirin in chronic HCV infection varies. This study aimed at investigating the pre- and on-treatment predictors of sustained virologic response (SVR) in patients with chronic hepatitis C (CHC) infection. PATIENTS AND METHODS: Clinical data of 48 patients with CHC treated with standard HCV antiviral combination therapy, between January 2005 and December 2010, at a Saudi University hospital, were retrospectively reviewed for age, sex, body mass index, liver enzymes, HCV-RNA viral load, liver biopsy, and response to treatment. The primary end point was SVR defined as undetectable HCV-RNA by polymerase chain reaction (PCR) 24 weeks after the end of treatment. Univariable logistic regression was used to explore the association between the different variables and SVR. These independent predictors of SVR were then analyzed with multivariable logistic regression analysis. RESULTS: Of the 48 treated patients, 25 (52%) were females and 27 (56%) were Saudi. The mean age was 43 years (43 +/- 10 years). Twenty-four (50%) had genotype-4, and 26 (54%) had liver biopsy. The overall SVR rate was 75% (36/48) and was 83.3% (20/24) among genotype-4 patients. Baseline factors associated with SVR identified by univariate logistic regression were genotype-4 and early viral response (EVR), defined as a drop of ≥ 2 log in serum HCV viral load after 12 weeks of initiation of combination therapy (P = 0.001). However, in stepwise regression analysis, the independent factor associated with the effect of antiviral therapy was genotype-4. When on-treatment variables were included, EVR (P = 0.003) and low baseline viral load (P = 0.048) were highly predictive of SVR. CONCLUSIONS: Of our HCV-treated patients, 75% had SVR. HCV genotype-4, EVR, and low baseline viral load were predictive of SVR.

[830]

TÍTULO / TITLE: - A prostate-specific antigen doubling time of <6 months is prognostic for metastasis and prostate cancer-specific death for patients receiving salvage radiation therapy post radical prostatectomy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Radiat Oncol. 2013 Jul 8;8:170. doi: 10.1186/1748-717X-8-170.

●● Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-170](#)

AUTORES / AUTHORS: - Jackson WC; Johnson SB; Li D; Foster C; Foster B; Song Y; Schipper M; Shilkrut M; Sandler HM; Morgan TM; Palapattu GS; Hamstra DA; Feng FY

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, University of Michigan, 1500 E. Medical Center Dr., Ann Arbor, MI 48105, USA.

RESUMEN / SUMMARY: - BACKGROUND: The ideal prostate-specific antigen (PSA) doubling time (PSADT) threshold for identifying patients at high-risk for poor clinical outcome following salvage radiation therapy (SRT) has not been well established. We sought to assess what PSADT threshold is most clinically prognostic in this setting. METHODS: 575 patients who received SRT at a single institution for biochemical recurrence after radical prostatectomy were retrospectively reviewed. We assessed the impact of pre-SRT PSADT on biochemical failure (BF), distant metastasis (DM), prostate cancer-specific mortality (PCSM), and overall mortality (OM). Kaplan-Meier methods, hazard ratio (HR) assessment, and Cox Proportional Hazard models were used to assess the discriminatory ability of various PSADT thresholds. RESULTS: Sufficient data to calculate PSADTs were available for 277 patients. PSADT was prognostic for BF, DM, PCSM, and OM on univariate analysis regardless of threshold. HR assessment identified 6 months as a strong threshold. No statistically significant difference was observed in BF, DM, PCSM, or OM between patients with PSADT <3 (n=40) and 3-6 months (n=61) or between 6-10 (n=62) and >10 months (n=114). However significant differences were seen in BF (HR:2.2, [95%CI: 1.4-3.5], p<0.01) and DM (HR:2.2, [95%CI: 1.2-4.3], p=0.02) between a PSADT of 3-6 and 6-10 months. On multivariate analysis a PSADT <6 months predicted BF (HR:2.0, [95%CI: 1.4-2.9], p=0.0001), DM (HR:2.0, [95%CI: 1.2-3.4], p=0.01), and PCSM (HR:2.6, [95%CI: 1.1-5.9], p=0.02). CONCLUSIONS: A pre-SRT PSADT <6 months was a strong predictor of outcomes in our data set, including PCSM. The most common nomogram for SRT uses a 10-month PSADT threshold for assigning points used to assess BF following SRT. If validated, our findings suggest that a PSADT threshold of <6 months should be considered for stratification of patients in future clinical trials in this setting.

[831]

TÍTULO / TITLE: - Multiple copies of BCR-ABL fusion gene on two isodicentric Philadelphia chromosomes in an imatinib mesylate-resistant chronic myeloid leukemia patient.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2013 May;5(5):1579-1582. Epub 2013 Mar 5.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1225](#)

AUTORES / AUTHORS: - Al-Achkar W; Wafa A; Moassass F; Klein E; Liehr T

INSTITUCIÓN / INSTITUTION: - Department of Molecular Biology and Biotechnology, Human Genetics Division, Atomic Energy Commission, Damascus, Syria ;

RESUMEN / SUMMARY: - The so-called Philadelphia (Ph) chromosome is present in more than 90% of chronic myeloid leukemia (CML) cases. Amplification or duplication of the BCR-ABL gene has been found to be one of the key factors leading to drug resistance to imatinib mesylate (IM). In the present study, we identified the presence of isodicentric Ph chromosomes [idic(Ph)] in an IM-resistant patient. Fluorescence in situ hybridization (FISH) analysis on metaphase chromosomes confirmed the heterogeneity and amplification of the fused BCR-ABL gene. FISH analysis superimposed on G-banding confirmed the presence of idic(Ph) chromosomes. Reverse transcription-polymerase chain reaction (RT-PCR) products revealed the presence of the BCR-ABL fusion transcript b3a2. The idic(Ph) chromosomes in CML were shown to be fused at the satellite regions of the short arms. The patient did not respond to IM chemotherapy and did not achieve remission. In this study, the impact of the idic(Ph) chromosomes on genomic instability, heterogeneity and amplification of the BCR-ABL gene in IM-resistant patients is discussed.

[832]

TÍTULO / TITLE: - Associations of ABCB1 and XPC Genetic Polymorphisms with Susceptibility to Colorectal Cancer and Therapeutic Prognosis in a Chinese Population.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(5):3085-91.

AUTORES / AUTHORS: - Yue AM; Xie ZB; Zhao HF; Guo SP; Shen YH; Wang HP

INSTITUCIÓN / INSTITUTION: - Oncological Surgery Department of Xinxiang Central Hospital, Xinxiang, Henan, China E-mail : aiminyue@163.com.

RESUMEN / SUMMARY: - Associations between ABCB1 and XPC genetic polymorphisms and risk of developing colorectal cancer (CRC) as well as clinical outcomes in CRCs with chemotherapy were investigated. A case-control study was performed on the ABCB1 C3435T, G2677T/A and XPC Lys939Gln polymorphisms in 428 CRC cases and 450 hospital- based, age and sex frequency-matched controls using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays. We observed that the ABCB1 3435CT or CC+CT variants were significantly linked with increasing risk of developing CRC (adjusted OR (95% CI): 1.814 (1.237-2.660), P=0.0022; adjusted OR (95% CI): 1.605 (1.117-2.306), P=0.0102, respectively). Moreover, the distribution frequency of XPC AC genotype or AC+CC genotypes also showed a tendency towards increasing the susceptibility for CRC (P=0.0759 and P=0.0903, respectively). Kaplan-Meier curves showed that the ABCB1 C3435T variant was associated with a tendency toward longer progression-free survival (PFS) (n=343, Log-rank test: P=0.063), and the G2677T/A variant genotypes

(GT+TT+GA+AA) with a tendency for longer OS in postoperative oxaliplatin-based patients (n=343, Log-rank test: P=0.082). However, no correlation of the XPC Lys939Gln polymorphism was found with PFS and OS in patients with postoperative oxaliplatin-based chemotherapy (n=343). Our study indicated that ABCB1 polymorphisms might be candidate pharmacogenomic factors for the prediction of CRC susceptibility, but not for prognosis with oxaliplatin chemosensitivity in CRC patients.

[833]

TÍTULO / TITLE: - Evaluation of preoperative C-reactive protein aids in predicting poor survival in patients with curative colorectal cancer with poor lymph node assessment.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2013 Jun;5(6):1881-1888. Epub 2013 Apr 16.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2013.1308](#)

AUTORES / AUTHORS: - Toiyama Y; Fujikawa H; Koike Y; Saigusa S; Inoue Y; Tanaka K; Mohri Y; Miki C; Kusunoki M

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan.

RESUMEN / SUMMARY: - Lymph node status is the most significant prognostic factor of colorectal cancer. However, there is a risk of disease understaging if the extent of lymph node assessment is sub-optimal. Preoperative C-reactive protein (CRP) is known to be a useful tool in predicting postoperative outcomes in patients with colorectal cancer. We retrospectively evaluated whether CRP adds to prognosis information in stage I-III colorectal cancer patients with poor lymph node assessment. In stages I-III, multivariate analysis revealed that CRP-positive status and advanced T-stage were factors that independently affected survival. In stage III, univariate analysis revealed that lymph node number retrieval and lymph node ratio were factors that affected survival. However, CRP positivity was the only independent factor for survival. CRP positivity did not predict poor prognosis in stage II or III patients with adequate lymph node retrieval. By contrast, the prognosis of CRP-positive patients was poorer than that of CRP-negative patients in stage II and III, with inadequate lymph node retrieval. CRP is an independent prognostic marker in patients with stage I-III, II or III colorectal cancer. The evaluation of CRP may provide useful information on prognosis in curative patients with an inadequate examination of lymph nodes.

[834]

TÍTULO / TITLE: - A Phase II Safety and Efficacy Study of the Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor Pazopanib in Patients With Metastatic Urothelial Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Genitourin Cancer. 2013 Jul 25. pii: S1558-7673(13)00136-5. doi: 10.1016/j.clgc.2013.05.005.

●● Enlace al texto completo (gratis o de pago) [1016/j.clgc.2013.05.005](#)

AUTORES / AUTHORS: - Pili R; Qin R; Flynn PJ; Picus J; Millward M; Ho WM; Pitot H; Tan W; Miles KM; Erlichman C; Vaishampayan U

INSTITUCIÓN / INSTITUTION: - Roswell Park Cancer Institute, Buffalo, NY.
Electronic address: Roberto.Pili@RoswellPark.org.

RESUMEN / SUMMARY: - BACKGROUND: Vascular endothelial growth factor (VEGF) is produced by bladder cancer cell lines in vitro and expressed in human bladder tumor tissues. Pazopanib is a vascular endothelial receptor tyrosine kinase inhibitor with anti-angiogenesis and anti-tumor activity in several preclinical models. A 2-stage phase II study was conducted to assess the activity and toxicity profile of pazopanib in patients with metastatic, urothelial carcinoma. METHODS: Patients with one prior systemic therapy for metastatic urothelial carcinoma were eligible. Patients received pazopanib at a dose of 800 mg orally for a 4-week cycle. RESULTS: Nineteen patients were enrolled. No grade 4 or 5 events were experienced. Nine patients experienced 11 grade 3 adverse events. Most common toxicities were anemia, thrombocytopenia, leucopenia, and fatigue. For stage I, none of the first 16 evaluable patients were deemed a success (complete response or partial response) by the Response Evaluation Criteria In Solid Tumors criteria during the first four 4-week cycles of treatment. Median progression-free survival was 1.9 months. This met the futility stopping rule of interim analysis, and therefore the trial was recommended to be permanently closed. CONCLUSIONS: Pazopanib did not show significant activity in patients with urothelial carcinoma. The role of anti-VEGF therapies in urothelial carcinoma may need further evaluation in rational combination strategies.

[835]

TÍTULO / TITLE: - Axillary lymph node status, adjusted for pathologic complete response in breast and axilla after neoadjuvant chemotherapy, predicts differential disease-free survival in breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Curr Oncol. 2013 Jun;20(3):e180-92. doi: 10.3747/co.20.1294.

●● Enlace al texto completo (gratis o de pago) [3747/co.20.1294](#)

AUTORES / AUTHORS: - Zhang GC; Zhang YF; Xu FP; Qian XK; Guo ZB; Ren CY; Yao M

INSTITUCIÓN / INSTITUTION: - Department of Breast Cancer, Cancer Center, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, PR China. ; Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX, U.S.A.

RESUMEN / SUMMARY: - BACKGROUND: Our retrospective study in breast cancer patients evaluated whether integrating subtype and pathologic complete response (pcr) information into axillary lymph node restaging after neoadjuvant chemotherapy (nac) adds significance to its prognostic values. METHODS: Patients included in the analysis had stage ii or iii disease, with post-nac axillary lymph node dissection (alnd), without sentinel lymph node biopsy before completion of nac, with definitive subtyping data and subtype-oriented adjuvant treatments. The ypN grading system was used to restage axillary lymph node status, and ypN0 was adjusted by pcr in both breast and axilla into ypN0(pcr) and ypN0(non-pcr). Univariate and multivariate survival analyses were performed. RESULTS: Among the 301 patients analyzed, 145 had tumours that were hormone receptor-positive (hr+) and negative for the human epidermal growth factor receptor (her2-), 101 had tumours that were positive for her2 (her2+), and 55 had tumours that were triple-negative. The rate of pcr in both breast and axilla was 11.7%, 43.6%, and 25.5% respectively for the 3 subtypes. Compared with the non-pcr patients, the pcr patients had better disease-free survival (dfs) and overall survival (os): p = 0.002 for dfs and p = 0.011 for os. In non-pcr patients, dfs and os were similar in the ypN0(non-pcr) and ypN1 subgroups, and in the ypN2 and ypN3 subgroups. We therefore grouped the ypN grading results into ypN0(pcr) (n = 75), ypN0-1(non-pcr) (n = 175), and ypN2-3 (n = 51). In those groups, the 3-year dfs was 98%, 91%, and 56%, and the 3-year os was 100%, 91%, and 82% respectively. The differences in dfs and os between those three subgroups were significant (all p < 0.05 in paired comparisons). Multivariate Cox regression showed that subtype and ypN staging adjusted by pcr were the only two independent factors predicting dfs. CONCLUSIONS: Axillary lymph node status after nac, adjusted for pcr in breast and axilla, predicts differential dfs in patients without prior sentinel lymph node biopsy.

[836]

TÍTULO / TITLE: - Introduction and First Clinical Application of a Simplified Immunohistochemical Validation System Confirms Prognostic Impact of KI-67 and CK20 for Stage T1 Urothelial Bladder Carcinoma: Single-Center Analysis of Eight Biomarkers in a Series of Three Hundred Six Patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Genitourin Cancer. 2013 Jul 10. pii: S1558-7673(13)00132-8. doi: 10.1016/j.clgc.2013.05.001.

●● Enlace al texto completo (gratis o de pago) 1016/j.clgc.2013.05.001

AUTORES / AUTHORS: - Otto W; Denzinger S; Fritsche HM; Burger M; Rossler W; Bertz S; May M; Hartmann A; Hofstadter F; Wieland WF; Eder F

INSTITUCIÓN / INSTITUTION: - St. Josef Medical Centre, Department of Urology of Regensburg University, Regensburg, Germany. Electronic address: wolfgang.otto@klinik.uni-regensburg.de.

RESUMEN / SUMMARY: - BACKGROUND: Biomarkers could help to estimate the prognosis of solid tumors. One of the reasons that many immunohistochemical (IHC) markers are not used routinely is the high interobserver variability and various cutoff values. In the present study, we used a simplified IHC method with a group of 8 biomarkers in stage pT1 urothelial bladder carcinoma (UBC). PATIENTS AND METHODS: IHC expression of CK20, KI-67, STK15, MUC7, periostin, fibronectin, survivin, and CXCR4 was assessed independently by 2 reviewers in a series of 306 stage pT1 UBC specimens from a single center in 10% steps from < 10% up to > 90%. A general center < 10% vs. >= 10% was set for further analysis for all markers. All patients initially underwent a bladder-sparing approach. Kaplan-Meier analyses and multivariate Cox regression analyses of recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS) were performed. RESULTS: A cutoff point >= 10% was shown to be valid and reliable for marker expression, with 96% interobserver agreement. Of the studied marker expressions, >= 10% for Ki-67 showed a statistically significant worse RFS (54% vs. 64%; P = .004), PFS (66% vs. 73%; P = .001), and CSS (71% vs. 77%; P = .015); >= 10% for CK20 showed a worse RFS (57% vs. 58%; P = .009). Multivariate Cox regression analysis revealed CK20 to be an independent prognostic factor for recurrence (hazard ratio [HR], 2.08; confidence interval [95% CI]; 1.21-3.57; P = .008) and Ki-67 for progression (HR, 2.11; CI, 1.02-4.37; P = .045). CONCLUSION: We proposed and applied a simplified IHC evaluation that increases interobserver agreement and confirms the prognostic role of Ki-67 and CK20 for stage T1 UBC.

[837]

TÍTULO / TITLE: - Association between genomic recurrence risk and well-being among breast cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jun 18;13(1):295.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-295](#)

AUTORES / AUTHORS: - Retel VP; Groothuis-Oudshoorn CG; Aaronson NK; Brewer NT; Rutgers EJ; van Harten WH

RESUMEN / SUMMARY: - BACKGROUND: Gene expression profiling (GEP) is increasingly used in the rapidly evolving field of personalized medicine. We sought to evaluate the association between GEP-assessed of breast cancer recurrence risk and patients' well-being. METHODS: Participants were Dutch women from 10 hospitals being treated for early stage breast cancer who were enrolled in the MINDACT trial (Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy). As part of the trial, they received a disease recurrence risk estimate based on a 70-gene signature and on standard clinical criteria as scored via a modified version of Adjuvant! Online. Women completed a questionnaire 6--8 weeks after surgery and after their decision regarding adjuvant chemotherapy. The questionnaire assessed

perceived understanding, knowledge, risk perception, satisfaction, distress, cancer worry and health-related quality of life (HRQoL), 6--8 weeks after surgery and decision regarding adjuvant chemotherapy. RESULTS: Women (n = 347, response rate 62%) reported high satisfaction with and a good understanding of the GEP information they received. Women with low risk estimates from both the standard and genomic tests reported the lowest distress levels. Distress was higher predominately among patients who had received high genomic risk estimates, who did not receive genomic risk estimates, or who received conflicting estimates based on genomic and clinical criteria. Cancer worry was highest for patients with higher risk perceptions and lower satisfaction. Patients with concordant high-risk profiles and those for whom such profiles were not available reported lower quality of life. CONCLUSION: Patients were generally satisfied with the information they received about recurrence risk based on genomic testing. Some types of genomic test results were associated with greater distress levels, but not with cancer worry or HRQoL. Trial registration: ISRCTN: ISRCTN18543567.

[838]

TÍTULO / TITLE: - EGFR ligands as pharmacodynamic biomarkers in metastatic colorectal cancer patients treated with cetuximab and irinotecan.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Target Oncol. 2013 Jul 3.

●● Enlace al texto completo (gratis o de pago) [1007/s11523-013-0284-](http://1007/s11523-013-0284-7)

[7](#)

AUTORES / AUTHORS: - Loupakis F; Cremolini C; Fioravanti A; Orlandi P; Salvatore L; Masi G; Schirripa M; Di Desidero T; Antoniotti C; Canu B; Faviana P; Sensi E; Lupi C; Fontanini G; Basolo F; Di Paolo A; Danesi R; Falcone A; Bocci G

INSTITUCIÓN / INSTITUTION: - Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana, Istituto Toscano Tumori, Via Roma 67, 56126, Pisa, Italy.

RESUMEN / SUMMARY: - This study was conducted to describe the modulation of plasma epidermal growth factor receptor (EGFR) ligands in EGFR-positive metastatic colorectal cancer (mCRC) patients during treatment with cetuximab and irinotecan and to explore the clinical implication of plasma levels' variations as potential biomarkers of benefit. Plasma amphiregulin (AR), epidermal growth factor (EGF), transforming growth factor-alpha, and heparin binding-EGF were assessed by ELISA in 45 chemorefractory mCRC patients, treated with cetuximab and irinotecan. Plasma levels were measured before and 1 h after the first administration of cetuximab, before and 1 h after the second administration, and before the third and the fifth cycles. KRAS and BRAF mutational status were determined. EGFR ligands' levels were differently modulated according to tumor KRAS and BRAF mutational status. In KRAS wild-type patients (n = 34), AR and EGF early increased and higher increases were significantly associated with worse clinical outcome. By adopting a specific

cut-off value, patients with higher levels of AR 1 h after the first administration had significantly worse response rate, progression free survival, and overall survival. This hypothesis-generating study shows that EGFR ligands are significantly modulated by cetuximab plus irinotecan according to KRAS and BRAF mutational status, and they warrant further investigation as pharmacodynamic markers of resistance to anti-EGFRs.

[839]

TÍTULO / TITLE: - Cost per patient and potential budget implications of denosumab compared with zoledronic acid in adults with bone metastases from solid tumours who are at risk of skeletal-related events: an analysis for Austria, Sweden and Switzerland.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Eur J Hosp Pharm Sci Pract. 2013 Aug;20(4):227-231. Epub 2013 Feb 21.

●● Enlace al texto completo (gratis o de pago) 1136/ejhpharm-2012-000235

AUTORES / AUTHORS: - Lothgren M; Ribnicsek E; Schmidt L; Habacher W; Lundkvist J; Pfeil AM; Biteeva I; Vrouchou P; Bracco A

INSTITUCIÓN / INSTITUTION: - International Health Economics and Reimbursement, Amgen (Europe) GmbH, Zug, Switzerland.

RESUMEN / SUMMARY: - **OBJECTIVES:** To assess cost implications per patient, per year, and to predict the potential annual budget impact when patients with bone metastases secondary to solid tumours at risk of skeletal-related events (SREs) transition from zoledronic acid (ZA; 4 mg every 3-4 weeks) to denosumab (120 mg every 4 weeks) in Austria, Sweden and Switzerland. **METHODS:** Country specific costs for medication and administration, patient management and SREs (defined as pathologic fracture, radiation to bone, surgery to bone and spinal cord compression) were assessed over a 1-year time horizon. Drug administration and patient management costs were taken from available public sources. SRE costs were based on local unit costs applied to country specific healthcare resources obtained from a multinational retrospective chart review study. Due to lack of real world data for the included countries, SRE rates were derived from phase III clinical trials in patients with advanced cancer and bone metastases. These trials demonstrated that denosumab was superior to ZA in the reduction of SREs. **RESULTS:** Estimated total annual cost savings for each patient transitioned from ZA to denosumab varied by country and cancer type, ranging from euro1583 to euro2375 in Austria, from euro1980 to euro2319 in Sweden (9.1 SEK/euro) and from euro3408 to euro3857 in Switzerland (1.2 CHF/euro). Cost savings were mainly driven by the lower SRE related costs and lower administration costs of denosumab compared with ZA. **CONCLUSIONS:** Denosumab offers superior efficacy compared with ZA in patients with solid tumours and bone metastases.

Cost savings are predicted in the Austrian, Swedish and Swiss healthcare systems following treatment transition from ZA to denosumab.

[840]

TÍTULO / TITLE: - Clinical and Prognostic Implications of Transcription Factor SOX4 in Patients with Colon Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 27;8(6):e67128. Print 2013.

- [Enlace al texto completo \(gratis o de pago\)](#)

1371/journal.pone.0067128

AUTORES / AUTHORS: - Lin CM; Fang CL; Hseu YC; Chen CL; Wang JW; Hsu SL; Tu MD; Hung ST; Tai C; Uen YH; Lin KY

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan ; Orthopedics Research Center, Taipei Medical University Hospital, Taipei, Taiwan.

RESUMEN / SUMMARY: - Colon cancer is one of the most common malignant cancers worldwide but the current therapeutic approaches for advanced colon cancer are less efficient. This study investigated associations between the expression of nuclear transcription factor SOX4 and various clinicopathologic parameters as well as patients' survival. Expression levels of nuclear SOX4 were analyzed by immunohistochemistry; the data comprised colon tissues from 263 patients with colon cancer. Paired t tests were used to analyze the differences in nuclear SOX4 expression between tumor and non-tumor tissues from each patient. Two-tailed Chi2 tests were performed to determine whether the differences in nuclear SOX4 expression and clinicopathologic parameters were significant. Time-to-event endpoints for clinicopathologic parameters were plotted using the Kaplan-Meier method, and statistical significance was determined using univariate log-rank tests. Cox proportional hazard model was used for multivariate analysis to determine the independence of prognostic effects of nuclear SOX4 expression. Overexpression of nuclear SOX4 was significantly correlated with depth of invasion ($P = 0.0041$), distant metastasis ($P < 0.0001$), and stage ($P = 0.0001$). Patients who displayed high expression levels of nuclear SOX4 achieved a significantly poorer disease-free survival rate, compared with patients with low SOX4 expression levels ($P < 0.001$). Univariate Cox regression analysis showed that overexpression of nuclear SOX4 was a clear prognostic marker for colon cancer ($P = 0.001$). Overexpression of nuclear SOX4 may be used as a marker to predict the outcome of patients with colon cancer.

[841]

TÍTULO / TITLE: - Clinical significance of serum-soluble interleukin-2 receptor in patients with follicular lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Aug;13(4):410-6. doi: 10.1016/j.clml.2013.03.014. Epub 2013 Jun 5.

●● Enlace al texto completo (gratis o de pago) [1016/j.clml.2013.03.014](https://doi.org/10.1016/j.clml.2013.03.014)

AUTORES / AUTHORS: - Yoshizato T; Nannya Y; Imai Y; Ichikawa M; Kurokawa M

INSTITUCIÓN / INSTITUTION: - Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Although sIL-2R level has a prognostic value in patients with diffuse large B-cell lymphoma, its clinical role in patients with follicular lymphoma has not been determined. PATIENTS AND METHODS: We reviewed data on 70 patients diagnosed with follicular lymphoma. RESULTS: Ann Arbor stage was I, II, III, and IV in 6, 9, 17, and 38 patients, respectively, and grade classification according to the World Health Organization criteria was 1, 2, 3^a, 3B, and not available in 28, 15, 11, 4, and 12 patients, respectively. sIL-2R at diagnosis was significantly correlated with Ann Arbor stages ($P < .001$), number of nodal lesions (≥ 5 or not) ($P = .0050$), and Follicular Lymphoma International Prognosis Index risk classification ($P = .0015$). Furthermore, sIL-2R regressed significantly in patients who achieved complete remission, uncertain complete remission, or partial remission ($P < .001$), and increased when regrowth of lymphoma was shown ($P < .001$). Finally, a high level of sIL-2R at diagnosis was correlated with shorter progression-free survival ($P = .018$) and time to next treatment ($P < .001$). CONCLUSION: Serum-soluble interleukin-2 receptor is correlated with tumor burden at diagnosis and during the clinical course of therapies in patients with follicular lymphoma, and our data support its usefulness to function as a surrogate marker of tumor progression.

[842]

TÍTULO / TITLE: - Expression of Secreted Protein Acidic and Rich in Cysteine in the Stroma of a Colorectal Carcinoma is Associated With Patient Prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Ann Coloproctol. 2013 Jun;29(3):93-9. doi: 10.3393/ac.2013.29.3.93. Epub 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [3393/ac.2013.29.3.93](https://doi.org/10.3393/ac.2013.29.3.93)

AUTORES / AUTHORS: - Kim JY; Jeong D; Ahn TS; Kim HJ; Park DS; Park SY; Bae SB; Lee S; Lee SS; Lee MS; Cho HD; Baek MJ

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Soonchunhyang University College of Medicine, Cheonan, Korea.

RESUMEN / SUMMARY: - PURPOSE: Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or basement-membrane-40 (BM-40), is a member of a family of matricellular proteins, whose functions are to modulate cell-matrix interactions, growth and angiogenesis in colorectal cancer. In this study, the expression of SPARC was evaluated and its correlations with clinicopathological parameters were investigated. METHODS: The researchers

analyzed the expression patterns of SPARC by using immunohistochemistry in 332 cases of colorectal cancer of tissue microarray. The clinicopathological characteristics were defined by using the TNM criteria of the Union for International Cancer Control. Clinicopathological factors such as age, sex, histologic type of the tumor, pathologic tumor stage, TNM stage, and lymphovascular invasion were evaluated according to the SPARC expression. RESULTS: The hazard ratios expressing SPARC in tumor cells, in the stroma, and in both tumor cells and the stroma were 2.10 (P = 0.036), 3.27 (P = 0.003) and 2.12 (P = 0.038), respectively. Patient survival was decreased in patient expressing SPARC in the stroma, and this result showed statistical significance (P = 0.016). CONCLUSION: These findings suggest that SPARC expression in a tumor and in the stroma correlates with disease progression and may be used as a prognostic marker for colorectal cancer.

[843]

TÍTULO / TITLE: - Intratumoral localization and activity of 17beta-hydroxysteroid dehydrogenase type 1 in non-small cell lung cancer: a potent prognostic factor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Transl Med. 2013 Jul 9;11:167. doi: 10.1186/1479-5876-11-167.

●● Enlace al texto completo (gratis o de pago) [1186/1479-5876-11-167](#)

AUTORES / AUTHORS: - Verma MK; Miki Y; Abe K; Suzuki T; Niikawa H; Suzuki S; Kondo T; Sasano H

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Japan.

RESUMEN / SUMMARY: - BACKGROUND: Estrogens were recently demonstrated to be synthesized in non-small cell lung carcinomas (NSCLCs) via aromatase activity and aromatase inhibitor (AI) did suppressed estrogen receptor (ER) positive NSCLC growth. However, other enzymes involved in intratumoral production and metabolism of estrogens, i.e. 17beta-hydroxysteroid dehydrogenases (i.e. 17betaHSD1 and 17betaHSD2) and others have not been studied. Therefore, in this study, we examined the clinical/ biological significance of 17beta-hydroxysteroid dehydrogenases in NSCLCs.

METHODOLOGY: Archival materials obtained from 103 NSCLC patients were immunohistochemically evaluated using anti-17betaHSD1 and anti-17betaHSD2 antibodies. The findings of immunohistochemistry were then correlated with intratumoral estrone (E1) and estradiol (E2) concentration, clinicopathological factors and overall survival of the patients. We further employed NSCLC cell lines, A549 and LK87 to study the functional significance of 17betaHSD1, in vitro. RESULTS: A higher 17betaHSD1 immunoreactivity tended to be positively associated with aromatase (p=0.057) and tumor stage (p=0.055) whereas a higher 17betaHSD2 immunoreactivity was positively associated with a squamous cell and adenosquamous cell carcinomas subtypes (p=0.031), tumor stage (p=0.004), T factor of TNM classification (p=0.010),

maximum tumor diameter ($p=0.002$) and tended to be associated with N factor of TMN classification ($p=0.065$). A higher 17betaHSD1 immunoreactivity was also significantly associated with lower intratumoral E1 concentration ($p=0.040$) and a higher intratumoral E2/E1 concentration ratio ($p=0.028$). On the other hand a higher 17betaHSD2 immunoreactivity was significantly associated with higher intratumoral E1 concentration ($p=0.035$). Results of multivariate regression analysis demonstrated an increased 17betaHSD1 immunoreactivity in tumor cells as an independent negative prognostic factor (HR= 2.83, $p=0.007$). E1 treatment in 17betaHSD1 positive NSCLC cells, A549 and LK87, resulted in E2 production ($p<0.0001$) and enhanced cell proliferation, which was abrogated effectively by 17betaHSD1 siRNA knockdown ($p<0.0001$). In addition, aromatase inhibitor treatment resulted in 17betaHSD1 up regulation in both A549 and LK87 cells. CONCLUSION: Results of our present study suggest that 17betaHSD1 may be considered an important prognostic factor in NSCLC patients and targeting 17betaHSD1 activity may further improve the clinical response in estrogen responsive NSCLC patients.

[844]

TÍTULO / TITLE: - Reirradiation in progressive high-grade gliomas: outcome, role of concurrent chemotherapy, prognostic factors and validation of a new prognostic score with an independent patient cohort.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Radiat Oncol. 2013 Jul 3;8(1):161.

●● Enlace al texto completo (gratis o de pago) [1186/1748-717X-8-161](#)

AUTORES / AUTHORS: - Scholtyssek F; Zwiener I; Schlamann A; Seidel C; Meixensberger J; Bauer M; Hoffmann KT; Combs SE; von Bueren AO; Kortmann RD; Muller K

RESUMEN / SUMMARY: - Purposes: First, to evaluate outcome, the benefit of concurrent chemotherapy and prognostic factors in a cohort of sixty-four high-grade glioma patients who underwent a second course of radiation therapy at progression. Second, to validate a new prognostic score for overall survival after reirradiation of progressive gliomas with an independent patient cohort. Patients and methods: All patients underwent fractionated reirradiation with a median physical dose of 36 Gy. Median planned target volume was 110.4 ml. Thirty-six patients received concurrent chemotherapy consisting in 24/36 cases (67%) of carboplatin and etoposide and in 12/36 cases (33%) of temozolomide. We used the Kaplan Meier method, log rank test and proportional hazards regression analysis for statistical assessment. RESULTS: Median overall survival from the start of reirradiation was 7.7 +/- 0.7 months. Overall survival rates at 6 and 12 months were 60 +/- 6% and 24 +/- 6%, respectively. Despite relatively large target volumes we did not observe any major acute toxicity. Concurrent chemotherapy did not appear to improve outcome. In contrast, female gender, young age, WHO grade III histology,

favorable Karnofsky performance score and complete resection of the tumor prior to reirradiation were identified as positive prognostic factors for overall survival. We finally validated a recent suggestion for a prognostic score with our independent but small patient cohort. Our preliminary findings suggest that its ability to discriminate between different prognostic groups is limited.

CONCLUSIONS: Outcome of our patients was comparable to previous studies. Even in case of large target volumes reirradiation seems to be feasible without observing major toxicity. The benefit of concurrent chemotherapy is still elusive. A reassessment of the prognostic score, tested in this study, using a larger patient cohort is needed.

[845]

TÍTULO / TITLE: - Predictive impact of polymorphism of PNPLA3 on HCC development after interferon therapy in Japanese patients with chronic hepatitis C.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Springerplus. 2013 Jun 1;2(1):251. Print 2013 Dec.

●● Enlace al texto completo (gratis o de pago) [1186/2193-1801-2-251](#)

AUTORES / AUTHORS: - Moritou Y; Ikeda F; Iwasaki Y; Baba N; Takaguchi K; Senoh T; Nagano T; Takeuchi Y; Yasunaka T; Ohnishi H; Miyake Y; Takaki A; Nouse K; Yamamoto K

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Kagawa Prefectural Central Hospital, Takamatsu, Japan.

RESUMEN / SUMMARY: - The impact of single-nucleotide polymorphisms (SNP) of patatin-like phospholipase domain-containing protein 3 (PNPLA3) on development of hepatocellular carcinoma (HCC) is not clarified for Japanese patients with chronic hepatitis C. The present study investigated the associations of rs738409 PNPLA3 with HCC development after the antiviral therapy with peg-interferon and ribavirin for Japanese patients with hepatitis C virus serotype 1 and high viral load. Of the 271 patients enrolled in the study, 20 patients developed HCC, during a median follow-up period of 4.6 years. Multivariate analysis in the proportional hazards models revealed that sex, body mass index, platelet counts, and alpha feroprotein (AFP) had significant associations with HCC development ($p = 0.011$, 0.029 , 0.0002 , and 0.046 , respectively). Multivariate regression analysis revealed that PNPLA3 148 M was significantly associated with serum AFP level ($p = 0.032$), other than body mass index, platelet count, and alanine aminotransferase ($p = 0.0006$, 0.0002 , and 0.037 , respectively), and that serum AFP level was significantly associated with PNPLA3 148 M ($p = 0.017$). Serum AFP level is an important factor in predicting HCC development after the antiviral therapy for Japanese patients with chronic hepatitis C, the mechanism of which might involve its significant associations with the SNP genotype of PNPLA3.

[846]

TÍTULO / TITLE: - Comparative study analyzing survival and safety of bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed in chemotherapy-naive patients with advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jul 1;6:803-9. doi: 10.2147/OTT.S45906. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\) 2147/OTT.S45906](#)

AUTORES / AUTHORS: - Kader YA; Le Chevalier T; El-Nahas T; Sakr A

INSTITUCIÓN / INSTITUTION: - Department of Clinical Oncology, Cairo University, Cairo, Egypt.

RESUMEN / SUMMARY: - PURPOSE: The majority of Egyptian patients with lung cancer present at a late stage of the disease.

Bevacizumab/carboplatin/paclitaxel, as well as cisplatin plus pemetrexed, are both standard regimens for advanced non-squamous bronchogenic cancer. This study compares both regimens, in terms of efficacy and toxicity profile, in Egyptian patients. PATIENTS AND METHODS: This is a randomized Phase II study comparing toxicity profile and survival in 41 chemotherapy-naive patients with stage IIIB or IV non-squamous NSCLC, with an ECOG performance status of 0 to 2. The epidermal growth factor receptor (EGFR) mutation detection was performed prior to treatment of all patients. Patients in the first group received: bevacizumab 7.5 mg/m² on Day 1 and Day 15; carboplatin area under the curve-5 on Day 1; and paclitaxel 60 mg/m² on Day 1, Day 8, and Day 15 every 4 weeks. In the second group, patients received cisplatin 75 mg/m² and pemetrexed 500 mg/m² every 3 weeks. RESULTS: The combination of bevacizumab/carboplatin/paclitaxel demonstrated higher Grade III-IV toxicity than cisplatin/pemetrexed regarding sensory/motor neuropathy (P = 0.06), DVT (P = 0.23), proteinuria (P = 0.23), and hypertension (P = 0.11), as well as Grade II alopecia (P = 0.001); however, no significant difference in toxicities between both arms was recorded regarding nausea and vomiting (P = 0.66), hematological toxicity, febrile neutropenia (P = 1) and fatigue (P = 0.66). Progression-free survival was similar for both treatment arms with a median of 6 months (P = 0.978). Overall median survival was comparable in both arms, 16.07 months versus 16.01 months (P = 0.89). CONCLUSION: Bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed provided meaningful and comparable efficacy in advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation. No significant difference in toxicity was observed between both treatment arms, apart from bevacizumab/carboplatin/paclitaxel-related risks as DVT, hypertension, proteinuria, sensory/motor neuropathy, and alopecia.

[847]

TÍTULO / TITLE: - Modified cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with

improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer. 2013 Jul 2. doi: 10.1002/cncr.28209.

●● Enlace al texto completo (gratis o de pago) [1002/cncr.28209](#)

AUTORES / AUTHORS: - Kaseb AO; Shindoh J; Patt YZ; Roses RE; Zimmitti G; Lozano RD; Hassan MM; Hassabo HM; Curley SA; Aloia TA; Abbruzzese JL; Vauthey JN

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas.

RESUMEN / SUMMARY: - BACKGROUND: The purpose of this study was to evaluate the factors associated with response rate, resectability, and survival after cisplatin/interferon alpha-2b/doxorubicin/5-fluorouracil (PIAF) combination therapy in patients with initially unresectable hepatocellular carcinoma.

METHODS: The study included 2 groups of patients treated with conventional high-dose PIAF (n = 84) between 1994 and 2003 and those without hepatitis or cirrhosis treated with modified PIAF (n = 33) between 2003 and 2012.

Tolerance of chemotherapy, best radiographic response, rate of conversion to curative surgery, and overall survival were analyzed and compared between the 2 groups, and multivariate and logistic regression analyses were applied to identify predictors of response and survival. RESULTS: The modified PIAF group had a higher median number of PIAF cycles (4 versus 2, P = .049), higher objective response rate (36% versus 15%, P = .013), higher rate of conversion to curative surgery (33% versus 10%, P = .004), and longer median overall survival (21.3 versus 10.6 months, P = .002). Multivariate analyses confirmed that positive hepatitis B serology (hazard ratio [HR] = 1.68; 95% confidence interval [CI] = 1.08-2.59) and Eastern Cooperative Oncology Group performance status ≥ 2 (HR = 1.75; 95% CI = 1.04-2.93) were associated with worse survival whereas curative surgical resection after PIAF treatment (HR = 0.15; 95% CI = 0.07-0.35) was associated with improved survival.

CONCLUSIONS: In patients with initially unresectable hepatocellular carcinoma, the modified PIAF regimen in patients with no hepatitis or cirrhosis is associated with improved response, resectability, and survival. Cancer 2013 © 2013 American Cancer Society.

1070.95\$! TATATAT - Cancer

[848]

TÍTULO / TITLE: - Evaluation of potentially predictive markers for anti-angiogenic therapy with sunitinib in recurrent ovarian cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Transl Oncol. 2013 Jun 1;6(3):305-10. Print 2013 Jun.

AUTORES / AUTHORS: - Bauerschlag DO; Hilpert F; Meier W; Rau J; Meinhold-Heerlein I; Maass N; Dubois A; Sehouli J; Arnold N; Schem C; Oberg HH; Baumann K

INSTITUCIÓN / INSTITUTION: - Department of Gynecological Oncology, University Medical Center Aachen, RWTH, Aachen, Germany.

RESUMEN / SUMMARY: - INTRODUCTION: In ovarian cancer, new therapeutic strategies are needed because the vast majority of patients develop a recurrence and resistance to platinum derivatives. Attached to the AGO-OVAR2.11 study investigating the multityrosine kinase inhibitor sunitinib in recurrent platinum refractory ovarian cancers, this translational research project assesses the potential value of serum vascular endothelial growth factor (VEGF), soluble VEGF receptor-3 (sVEGFR-3), and angiopoietin-2 (Ang-2) levels for progression-free survival (PFS). MATERIALS AND METHODS: Longitudinal serum samples were taken while the patient was on study drugs. Serum concentration of VEGF, sVEGFR-3, and Ang-2 was determined by ELISA. The slope of the markers was correlated to the PFS. RESULTS: Patients showing a decrease in VEGF concentration had a median PFS of 10.5 months [confidence interval (CI), 2.89-12.25] compared to 2.9 months (CI, 1.48-5.32) in the case of an increase ($P = .17$). The stratified log-rank test showed a trend for longer PFS if a decrease of Ang-2 was observed ($P = .089$). Dichotomized in absolute decrease or increase, the PFS was 8.4 months (CI, 2.89-12.26) versus 2.7 months (CI, 1.05-5.32), respectively. Patients with a reduction of the sVEGFR-3 concentration had a median PFS of 4.76 months (CI 2.86-10.65) versus 8.61 months (CI, 1.05-not estimable) in patients with an increase of sVEGFR-3. This observation was statistically not significant in the log-rank test ($P = .81$). CONCLUSION: Ang-2 could potentially identify a patient population that might have a better PFS when under anti-angiogenic treatment, like the tyrosine kinase inhibitor sunitinib.

[849]

TÍTULO / TITLE: - Monitoring response to tyrosine kinase inhibitor therapy, mutational analysis, and new treatment options in chronic myelogenous leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Natl Compr Canc Netw. 2013 May;11(5 Suppl):663-6.

AUTORES / AUTHORS: - Radich JP

INSTITUCIÓN / INSTITUTION: - Molecular Oncology Lab, Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Seattle, Washington 98109-1024, USA. jradich@fhcrc.org

RESUMEN / SUMMARY: - Unlike in other leukemias, survival rates have climbed dramatically in early-phase chronic myelogenous leukemia (CML). This improvement in long-term prognosis is primarily the result of the tyrosine kinase inhibitor (TKI) imatinib and its second-generation cousins nilotinib and dasatinib. In his presentation at the NCCN 18th Annual Conference, Dr. Jerald P. Radich reviewed the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommendations for monitoring response to treatment with the TKIs, which center on complete cytogenetic response, and the role of

mutational analysis for guiding treatment decisions in the setting of imatinib resistance. He also offered a brief mention of 2 new agents recently approved for resistant CML—ponatinib and bosutinib.

[850]

TÍTULO / TITLE: - Juzentaihoto Failed to Augment Antigen-Specific Immunity but Prevented Deterioration of Patients' Conditions in Advanced Pancreatic Cancer under Personalized Peptide Vaccine.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:981717. doi: 10.1155/2013/981717. Epub 2013 Jun 10.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/981717](#)

AUTORES / AUTHORS: - Yutani S; Komatsu N; Matsueda S; Yoshitomi M; Shirahama T; Yamada A; Itoh K; Sasada T

INSTITUCIÓN / INSTITUTION: - Department of Immunology and Immunotherapy, Kurume University School of Medicine, Kurume 830-0011, Japan.

RESUMEN / SUMMARY: - Juzentaihoto (JTT) is a well-known Japanese herbal medicine, which has been reported to modulate immune responses and enhance antitumor immunity in animal models. However, it is not clear whether JTT has similar effects on humans. In particular, there is little information on the effects of JTT in antigen-specific immunity in cancer patients. Here we conducted a randomized clinical study to investigate whether combined usage of JTT could affect antigen-specific immunity and clinical findings in advanced pancreatic cancer patients undergoing personalized peptide vaccination (PPV), in which HLA-matched vaccine antigens were selected based on the preexisting host immunity. Fifty-seven patients were randomly assigned to receive PPV with (n = 28) or without (n = 29) JTT. Unexpectedly, JTT did not significantly affect cellular or humoral immune responses specific to the vaccine antigens, which were determined by antigen-specific interferon-gamma secretion in T cells and antigen-specific IgG titers in plasma, respectively. Nevertheless, JTT prevented deterioration of patients' conditions, such as anemia, lymphopenia, hypoalbuminemia, plasma IL-6 elevation, and reduction of performance status, which are frequently observed in advanced cancers. To our knowledge, this is the first clinical study that examined the immunological and clinical effects of JTT in cancer patients undergoing immunotherapy in humans.

[851]

TÍTULO / TITLE: - Predictive impact of common variations in DNA repair genes on clinical outcome of osteosarcoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(6):3677-80.

AUTORES / AUTHORS: - Bai SB; Chen HX; Bao YX; Luo X; Zhong JJ

INSTITUCIÓN / INSTITUTION: - Department of Anatomy and Neurobiology, Xiangya School of Medicine, Central South University, Changsha, China E-mail : baisb_777@126.com.

RESUMEN / SUMMARY: - We aimed to assess the role of XPG, XPC and MMS19L polymorphisms on response to chemotherapy in osteosarcomas, and the clinical outcomes. One hundred and eighty five osteosarcoma patients who were histologically confirmed were enrolled in our study between January 2007 and December 2009. Genotyping of XPG, XPC and MMS19L was performed in a 384-well plate format on the MassARRAY® platform. Individuals with XPG TT genotype and T allele were more likely to be better response to chemotherapy than CC genotype, with the OR (95% CI) of 4.17 (1.64-11.54) and 2.66 (1.39-5.11), respectively. Those carrying MMS19L TT genotype and T allele showed better response to chemotherapy, with ORs (95% CI) of 4.8 (1.56-17.7) and 2.3 (1.22-4.36), respectively. Patients carrying TT genotype of XPG and MMS19L showed a significantly longer overall survival than CC genotype, with a 0.47 and 0.30-fold risk of death when compared with the wild-type of the gene. XPG and MMS19L are correlated with response to chemotherapy and prognosis of osteosarcoma, so that they could be used as predictive markers for prognosis.

[852]

TÍTULO / TITLE: - Low Annexin A1 expression predicts benefit from induction chemotherapy in oral cancer patients with moderate or poor pathologic differentiation grade.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jun 21;13:301. doi: 10.1186/1471-2407-13-301.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1471-2407-13-301](#)

AUTORES / AUTHORS: - Zhu DW; Liu Y; Yang X; Yang CZ; Ma J; Yang X; Qiao JK; Wang LZ; Li J; Zhang CP; Zhang ZY; Zhong LP

INSTITUCIÓN / INSTITUTION: - Department of Oral & Maxillofacial-Head & Neck Oncology, Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, No,639 Zhizaoju Road, Shanghai 200011, China. wanglizhen9th@hotmail.com.

RESUMEN / SUMMARY: - BACKGROUND: The benefit of induction chemotherapy in locally advanced oral squamous cell carcinoma (OSCC) remains to be clearly defined. Induction chemotherapy is likely to be effective for biologically distinct subgroups of patients and biomarker development might lead to identification of the patients whose tumors are to respond to a particular treatment. Annexin A1 may serve as a biomarker for responsiveness to induction chemotherapy. The aim of this study was to investigate Annexin A1 expression in pre-treatment biopsies from a cohort of OSCC patients treated with surgery and post-operative radiotherapy or docetaxel, cisplatin and 5-fluorouracil (TPF) induction chemotherapy followed by surgery and post-operative radiotherapy.

Furthermore we sought to assess the utility of Annexin A1 as a prognostic or predictive biomarker. METHODS: Immunohistochemical staining for Annexin A1 was performed in pre-treatment biopsies from 232 of 256 clinical stage III/IVA OSCC patients. Annexin A1 index was estimated as the proportion of tumor cells (low and high, <50% and \geq 50% of stained cells, respectively) to Annexin A1 cellular membrane and cytoplasm staining. RESULTS: There was a significant correlation between Annexin A1 expression and pathologic differentiation grade ($P=0.015$) in OSCC patients. The proportion of patients with low Annexin A1 expression was significantly higher amongst those with moderate/poorly differentiated tumor (78/167) compared to those with well differentiated tumor (18/65). Multivariate Cox model analysis showed clinical stage ($P=0.001$) and Annexin A1 expression ($P=0.038$) as independent prognostic risk factors. Furthermore, a low Annexin A1 expression level was predictive of longer disease-free survival ($P=0.036$, HR=0.620) and locoregional recurrence-free survival ($P=0.031$, HR=0.607) compared to high Annexin A1 expression. Patients with moderate/poorly differentiated tumor and low Annexin A1 expression benefited from TPF induction chemotherapy as measured by distant metastasis-free survival ($P=0.048$, HR=0.373) as well as overall survival ($P=0.078$, HR=0.410). CONCLUSIONS: Annexin A1 can be used as a prognostic biomarker for OSCC. Patients with moderate/poorly differentiated OSCC and low Annexin A1 expression can benefit from the addition of TPF induction chemotherapy to surgery and post-operative radiotherapy. Annexin A1 expression can potentially be used as a predictive biomarker to select OSCC patients with moderate/poorly differentiated tumor who may benefit from TPF induction chemotherapy.

[853]

TÍTULO / TITLE: - Pharmacogenetic Influence of GST Polymorphisms on Anthracycline-Based Chemotherapy Responses and Toxicity in Breast Cancer Patients: A Multi-Analytical Approach.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Diagn Ther. 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) [1007/s40291-013-0045-](#)

[4](#)

AUTORES / AUTHORS: - Tulsyan S; Chaturvedi P; Agarwal G; Lal P; Agrawal S; Mittal RD; Mittal B

INSTITUCIÓN / INSTITUTION: - Department of Genetics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli road, Lucknow, 226 014, India.

RESUMEN / SUMMARY: - BACKGROUND AND OBJECTIVE: Chemotherapeutic drug treatment outcomes are genetically determined. Polymorphisms in genes encoding phase II drug metabolizing enzyme glutathione-S-transferase (GST) can possibly predict treatment outcomes, and can be of prognostic significance in breast cancer patients. The aim of this study was to determine the role of

genetic variations in GST in predicting response to, and toxicity of, anthracycline-based chemotherapy in breast cancer patients. **METHOD:** Two hundred and seven patients treated with anthracycline-based chemotherapy were genotyped for GSTM1 and GSTT1 deletion polymorphisms, and GSTP1 Ile105Val (rs1695), by polymerase chain reaction (PCR)/ PCR-restriction fragment length polymorphism (RFLP). Genetic variations were correlated with tumor response to neo-adjuvant chemotherapy (NACT) in 100 patients, and with chemo-toxicity in 207 who received adjuvant chemotherapy or NACT, using Chi-square and logistic regression. Higher order gene-gene interactions with treatment outcomes were characterized by multifactor dimensionality reduction (MDR) analysis. **RESULTS:** In single-locus analysis, Ile/Val and Ile/Val + Val/Val genotypes of the GSTP1 Ile105Val (rs1695) polymorphism reached statistical significance with grade 2-4 anemia ($P = 0.019$, $P = 0.027$). On performing gene-gene interaction analysis, GSTM1 null-GSTP1 Ile/Val was significantly associated with response to NACT ($P = 0.032$). On evaluating higher order gene-gene interaction models by MDR analysis, GSTM1 and GSTP1 Ile105Val; GSTM1 and GSTT1; and GSTT1 and GSTP1 Ile105Val showed significant association with treatment response, grade 2-4 anemia, and dose delay/reduction due to neutropenia ($P = 0.046$, $P = 0.027$, $P = 0.026$), respectively. **CONCLUSION:** Multi-analytical strategies may serve as a better tool for characterization of pharmacogenetic-based breast cancer treatment outcomes.

[854]

TÍTULO / TITLE: - Therapy-resistant acute lymphoblastic leukemia (ALL) cells inactivate FOXO3 to escape apoptosis induction by TRAIL and Noxa.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncotarget. 2013 Jul;4(7):995-1007.

AUTORES / AUTHORS: - Ausserlechner MJ; Salvador C; Deutschmann A; Bodner M; Viola G; Bortolozzi R; Basso G; Hagenbuchner J; Obexer P

INSTITUCIÓN / INSTITUTION: - Department of Pediatrics I, Medical University Innsbruck, Austria.

RESUMEN / SUMMARY: - Forkhead transcription factors (FOXO) are downstream targets of the phosphoinositol-3-kinase (PI3K) protein kinase B (PKB) signaling cascade and play a pivotal role in cell differentiation, cell cycle and apoptosis. We found that cells from prednisone-resistant T-acute lymphoblastic leukemia (T-ALL) patients showed cytoplasmic localization of FOXO3 in comparison to prednisone-sensitive patients suggesting its inactivation. To determine the impact of FOXO3, T-ALL cells were infected with a 4OH-tamoxifen-regulated, phosphorylation-independent FOXO3(A3)ERtm allele. After FOXO3-activation these cells undergo caspase-dependent apoptosis. FOXO3 induces the death ligand TRAIL and the BH3-only protein Noxa implicating extrinsic as well as intrinsic death signaling. Whereas dnFADD partially inhibited cell death, CrmA and dnBID efficiently rescued ALL cells after FOXO3 activation, suggesting a

caspase-8 amplifying feedback loop downstream of FADD. Knockdown of TRAIL and Noxa reduced FOXO3-induced apoptosis, implicating that mitochondrial destabilization amplifies TRAIL-signaling. The-reconstitution of the cell cycle inhibitor p16INK4A, which sensitizes ALL cells to mitochondria-induced cell death, represses FOXO3 protein levels and reduces the dependency of these leukemia cells on PI3K-PKB signaling. This suggests that if p16INK4A is deleted during leukemia development, FOXO3 levels elevate and FOXO3 has to be inactivated by deregulation of the PI3K-PKB pathway to prevent FOXO3-induced cell death.

[855]

TÍTULO / TITLE: - The prognostic significance of APC gene mutation and miR-21 expression in advanced stage colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Colorectal Dis. 2013 Jun 17. doi: 10.1111/codi.12318.

●● [Enlace al texto completo \(gratis o de pago\) 1111/codi.12318](#)

AUTORES / AUTHORS: - Chen TH; Chang SW; Huang CC; Wang KL; Yeh KT; Liu CN; Lee H; Lin CC; Cheng YW

INSTITUCIÓN / INSTITUTION: - Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; Division of Gastroenterology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan.

RESUMEN / SUMMARY: - AIM: Colorectal cancer (CRC) is the second commonest cause of cancer death in Taiwan. Although numerous genes have been associated with tumorigenesis in colorectal cancer, only a few have been validated and used as biomarkers for predicting clinical outcome. The aim of this study was to analyze the association of APC gene inactivation and miR-21 expression with clinical outcome in CRC patients. METHOD: 195 colorectal cancer patients were enrolled in a single medical center between 2003 and 2007. APC gene mutation and expression of APC and miR21 were analyzed by direct DNA sequencing and real-time RT-PCR. The primary outcome included 5-year overall survival, and univariate (Kaplan-Meier) and multivariate (Cox regression) analyses of prognostic factors. RESULTS: The results showed that 66 (33.8%) of 195 tumour tissues contained an APC mutation. The predominant APC gene variations were deletion mutations (50.0%). APC gene expression was low in CRC and negatively correlated with miR-21 expression and gene mutation. In advanced-stage cancer, patients with APC mutation/high miR-21 had poorer overall survival rates than those with APC mutation/low miR-21, APC wild-type/high miR-21, and APC wild-type/low miR-21. CONCLUSION: In Taiwan, down-regulation of the APC gene in CRC correlated with gene mutation and miR-21 upregulation. APC mutation and miR-21 expression could be used to predict the clinical outcome of CRC, especially in patients with advanced disease. This article is protected by copyright. All rights reserved.

[856]

TÍTULO / TITLE: - Double-positive expression of high-mobility group box 1 and vascular endothelial growth factor C indicates a poorer prognosis in gastric cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - World J Surg Oncol. 2013 Jul 18;11:161. doi: 10.1186/1477-7819-11-161.

●● Enlace al texto completo (gratis o de pago) [1186/1477-7819-11-161](#)

AUTORES / AUTHORS: - He W; Tang B; Yang D; Li Y; Song W; Cheang T; Chen X; Li Y; Chen L; Zhan W; Li W; He Y

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal and Pancreatic Surgery, The first Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, China. wenli28@163.com.

RESUMEN / SUMMARY: - BACKGROUND: Although many studies have indicated that high-mobility group box 1 protein (HMGB1) is associated with oncogenesis and a worse prognosis, the prognostic value of HMGB1 in gastric cancer (GC) remains unclear. In the present work, we aimed to evaluate the role of HMGB1 in GC and examined whether aberrant expression of both HMGB1 and vascular endothelial growth factor C (VEGF-C) increased the malignant potential of GC. METHODS: A total of 166 GC patients and 32 normal subjects were enrolled. HMGB1 and VEGF-C expression was detected by tissue microarrays (TMAs) and immunohistochemical staining. The correlation between HMGB1 and VEGF-C expression and their relationships with clinicopathological GC variables were examined. Univariate and multivariate analyses were performed using the Cox proportional hazard model to predict the factors related to the patients' overall survival rates. RESULTS: HMGB1 and VEGF-C expression were observed in 81 (48.80%) and 88 (53.01%) tumors, respectively, significantly higher than the rates among the corresponding controls. In addition, HMGB1 and VEGF-C expression were positively correlated ($R^2 = 0.972$). HMGB1 expression was also closely associated with tumor size, pT stage, nodal status, metastasis status, TNM stage, and poor prognosis. Multivariate survival analysis indicated that patients with HMGB1 and VEGF-C coexpression had the worst prognoses and survival rates (hazard ratio, 2.78; log rank $P < 0.001$). CONCLUSIONS: HMGB1 is commonly expressed in GC. Combined evaluation of HMGB1 and VEGF-C may serve as a valuable independent prognostic factor for GC patients.

[857]

TÍTULO / TITLE: - Prophylactic Lamivudine to Improve the Outcome of Breast Cancer Patients With HBsAg Positive During Chemotherapy: A Meta-Analysis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Hepat Mon. 2013 Apr 1;13(4):e6496. doi: 10.5812/hepatmon.6496. Print 2013 Apr.

●● Enlace al texto completo (gratis o de pago) [5812/hepatmon.6496](#)

AUTORES / AUTHORS: - Zheng Y; Zhang S; Tan Grahn HM; Ye C; Gong Z; Zhang Q

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, The First Affiliated Hospital, Wenzhou Medical College, Wenzhou, Zhejiang, China.

RESUMEN / SUMMARY: - **CONTEXT:** Raising the chemotherapy-induced HBV reactivation is parallel to the increment of chemotherapy treatments in breast cancer patients. This meta-analysis aims to evaluate the efficacy of prophylactic use of lamivudine in breast cancer patients with HBsAg positive during chemotherapy. **EVIDENCE ACQUISITION:** MEDLINE, Pubmed, Ovid and Embase were used to search for clinical studies comparing with or without prophylactic use of lamivudine for HBV reactivation in breast cancer patients receiving chemotherapy. Outcomes of interest were the rate of HBV reactivation, incidence of hepatitis and incidence of hepatitis attributable to HBV reactivation, severity of hepatitis and severity of hepatitis attributable to HBV reactivation, the rate of chemotherapy disruption, and the rate of chemotherapy disruption attributable to HBV reactivation, overall mortality, and mortality attributable to HBV reactivation. **RESULTS:** Four studies with 285 patients were included in this meta-analysis. The rate of HBV reactivation, incidence of hepatitis and incidence of hepatitis related to HBV reactivation were reduced by use of prophylactic lamivudine compared to control group. Pooled Odds Ratios (ORs) were 0.09 (95% confidence intervals [CI] 0.03-0.26; $P < 0.0001$), 0.23 (95% CI 0.06-0.92; $P = 0.04$), and 0.10 (95% CI 0.03-0.32; $P < 0.0001$) respectively. There was a reduction in chemotherapy disruption related to HBV reactivation by use of prophylactic lamivudine (pooled OR = 0.11; 95% CI 0.02-0.58; $P = 0.01$). Chemotherapy disruption, overall mortality, and mortality attributable to HBV reactivation were not significantly different between two groups. Pooled ORs were 0.42 (95% CI 0.11-1.58; $P = 0.20$), 0.37 (95% CI 0.07-2.04; $P = 0.25$), and 0.25 (95% CI 0.01-6.82; $P = 0.41$) respectively. Lamivudine was well-tolerated, and no additional toxicity was observed. **CONCLUSIONS:** Use of prophylactic lamivudine may have positive effect on the outcome of breast cancer patients with HBsAg positive during chemotherapy.

[858]

TÍTULO / TITLE: - Overexpressed transcription factor FOXM1 is a potential diagnostic and adverse prognostic factor in postoperational gastric cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Transl Oncol. 2013 Jul 20.

- [Enlace al texto completo \(gratuito o de pago\) 1007/s12094-013-1076-](#)

[3](#)

AUTORES / AUTHORS: - Li X; Qi W; Yao R; Tang D; Liang J

INSTITUCIÓN / INSTITUTION: - Department of Oncology of the Affiliated Hospital of Medical College Qingdao University, 16 Jiangsu Road, Qingdao, 266003, China.

RESUMEN / SUMMARY: - **PURPOSE:** In the present study, we intend to detect the expression of Forkhead box transcription (FOXM1) in gastric cancer tissues and cell lines, and analyze the correlation between FOXM1 expression and clinic-pathological features as well as their association with clinic outcomes in patients with resectable gastric cancers. **METHODS:** We examined the expression of FOXM1 in 103 cancer tissues from patients who underwent gastrectomy during Jan 2007 to Nov 2007 and 68 randomly selected para-cancer tissues by immunohistochemistry. The expression of FOXM1 protein in the benign and malignant human gastric cell lines was simultaneously detected using Western blot analysis. Data on clinic-pathological features and relevant prognostic factors in these patients were then analyzed. **RESULTS:** FOXM1 expression was absolutely higher in gastric cancer than para-cancer tissues ($P < 0.001$) and normal gastric epithelium cell lines ($P = 0.022$). No significant association was found between FOXM1 expression and any clinic-pathological parameters ($P > 0.1$). FOXM1 amplification was showed to be independently associated with prognosis in gastric cancer patients ($P = 0.001$), 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 ($P = 0.001$) as a result of stage-stratified analysis. **CONCLUSIONS:** Overexpressed FOXM1 is a potential diagnostic and poor prognostic biomarker in postoperational gastric cancer patients.

[859]

TÍTULO / TITLE: - Phase 1 study of intravenous rigosertib (ON 01910.Na), a novel benzyl styryl sulfone structure producing G2/M arrest and apoptosis, in adult patients with advanced cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Am J Cancer Res. 2013 Jun 20;3(3):323-38. Print 2013.

AUTORES / AUTHORS: - Ohnuma T; Lehrer D; Ren C; Cho SY; Maniar M; Silverman L; Sung M; Gretz HF 3rd; Benisovich V; Navada S; Akahoho E; Wilck E; Taft DR; Roboz J; Wilhelm F; Holland JF

INSTITUCIÓN / INSTITUTION: - Department of Radiology and Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai New York, NY, USA.

RESUMEN / SUMMARY: - Rigosertib (ON 01910.Na), a synthetic novel benzyl styryl sulfone, was administered to 28 patients with advanced cancer in a Phase I trial in order to characterize its pharmacokinetic profile, determine the dose-limiting toxicities (DLT), define the recommended phase II dose (RPTD) and to document any antitumor activity. Patients with advanced malignant neoplasms refractory to standard therapy were given escalating doses of rigosertib (50, 100, 150, 250, 325, 400, 650, 850, 1,050, 1,375, 1,700 mg/m²/24h) as a 3-day continuous infusion (CI) every 2 weeks. An accelerated Fibonacci titration schedule with specified decreases for toxicities was used for escalation until

grade ≥ 2 toxicity occurred. Inpatient dose escalation was allowed if toxicity was grade ≤ 2 and the disease remained stable. Plasma pharmacokinetics (PK) and urinary PK assessments were studied in the 1st and 4th cycles. Twenty-nine patients (12 men and 17 women; age 36-87 y with a median of 63 y) were registered, but one died before study drug was given. Twenty-eight patients received a median of 3 cycles of therapy. Most common grade ≥ 2 toxicities attributable to rigosertib included fatigue, anorexia, vomiting and constipation. DLTs included muscular weakness, hyponatremia, neutropenia, delirium and confusional state. Risk factors for severe toxicities include pre-existing neurological dysfunction or advanced gynecologic cancer after pelvic surgery. Rigosertib pharmacokinetics showed rapid plasma distribution phases and urinary excretion. Elevations in plasma C_{max} and AUC due to decreases in plasma clearance were associated with acute grade ≥ 3 toxicities. Of 22 evaluable patients, 9 (41%) achieved a best overall response of stable disease; all other patients (n=13; 59%) progressed. The median progression-free survival time was 50 days (95% confidence interval [CI]: 37-80 days). Nine (41%) patients survived for over 1 y. In summary, prolonged IV infusions of rigosertib were generally well tolerated. Nine (41%) patients achieved stable disease and 9 (41%) patients survived for over 1 year. The RPTD appears to be 850 mg/m²/24hr CI x 3 days. (ClinicalTrials.gov identifier: NCT01538537).

[860]

TÍTULO / TITLE: - Predictive value of PET-CT for pathological response in stages II and III breast cancer patients following neoadjuvant chemotherapy with docetaxel.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Rev Esp Med Nucl. Acceso gratuito al texto completo a partir de los 2 años de la fecha de publicación.

- Enlace a la Editora de la Revista <http://db.doyma.es/>

- Cita: Revista Española de Medicina Nuclear: <> Imagen Mol. 2013 Jun 25. pii: S2253-654X(13)00078-4. doi: 10.1016/j.remn.2013.04.008.

- Enlace al texto completo (gratis o de pago)

1016/j.remn.2013.04.008

AUTORES / AUTHORS: - Garcia Garcia-Esquinas MA; Arrazola Garcia J; Garcia-Saenz JA; Furio-Bacete V; Fuentes Ferrer ME; Ortega Candil A; Cabrera Martin MN; Carreras Delgado JL

INSTITUCIÓN / INSTITUTION: - Nuclear Medicine Department, Hospital Clinico San Carlos, Madrid, España; Radiology Department, Hospital Clinico San Carlos, Madrid, España. Electronic address: marta.garcia@gmx.de.

RESUMEN / SUMMARY: - PURPOSE: To prospectively study the value of PET-CT with fluorine-18 fluorodeoxyglucose (FDG) to predict neoadjuvant chemotherapy (NAC) response of locoregional disease of stages II and III breast cancer patients. MATERIAL AND METHODS: A written informed consent and approval were obtained from the Ethics Committee. PET-CT

accuracy in the prediction of pathologic complete response (pCR) after NAC was studied in primary tumors and lymph node metastasis in 43 women (mean age: 50 years; range: 27-71 years) with histologically proven breast cancer between December 2009 and January 2011. PET-CT was performed at baseline and after NAC. SUVmax percentage changes (DeltaSUVmax) were compared with pathology findings at surgery. Receiver-operator characteristic (ROC) analysis was used to discriminate between locoregional pCR and non-pCR. In patients not achieving pCR, it was investigated if DeltaSUVmax could accurately identify the residual cancer burden (RCB) classes: RCB-I (minimal residual disease (MRD)), RCB-II (moderate RD), and RCB-III (extensive RD). RESULTS: pCR was obtained in 11 patients (25.6%). Residual disease was found in 32 patients (74.4%): 16 (37.2%) RCB-I, 15 (35.6%) RCB-II and 2 (4.7%) RCB-III. Sensitivity, specificity, and accuracy to predict pCR were 90.9%, 90.6%, and 90.7%, respectively. Specificity was 94.1% in the identification of a subset of patients who had either pCR or MRD. CONCLUSION: Accuracy of DeltaSUVmax in the locoregional disease of stages II and III breast cancer patients after NAC is high for the identification of pCR cases. Its specificity is potentially sufficient to identify a subgroup of patients who could be managed with conservative surgery.

[861]

TÍTULO / TITLE: - Prognostic significance of the decreased rate of perioperative serum carcinoembryonic antigen level in the patients with colon cancer after a curative resection.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Ann Coloproctol. 2013 Jun;29(3):115-22. doi: 10.3393/ac.2013.29.3.115. Epub 2013 Jun 30.

●● [Enlace al texto completo \(gratis o de pago\) 3393/ac.2013.29.3.115](#)

AUTORES / AUTHORS: - Jung TD; Yoo JH; Lee MJ; Park HK; Shin JH; An MS; Ha TK; Kim KH; Bae KB; Kim TH; Choi CS; Oh MK; Hong KH

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea.

RESUMEN / SUMMARY: - PURPOSE: The serum level of carcinoembryonic antigen (CEA) is a clinical prognostic factor in the follow-up evaluation of patients with colon cancer. We aimed to evaluate the prognostic significance of the rate of decrease of the perioperative serum CEA level in patients with colon cancer after a curative resection. METHODS: A total of 605 patients who underwent a curative resection for colon cancer between January 2000 and December 2007 were enrolled retrospectively. The rate of decrease was calculated using the following equation: $([\text{preoperative CEA} - \text{postoperative CEA}] / [\text{preoperative CEA}] \times 100)$. RESULTS: In the group with a preoperative serum CEA level of >5 ng/mL, the normalized group with a postoperative serum CEA level of ≤ 5 ng/mL showed a better overall survival (OS) rate and disease-free survival (DFS) rate than those of the non-normalized group ($P \leq$

0.0001). The “cutoff values” of the rate of decrease in the perioperative serum CEA that determined the OS and the DFS were 48.9% and 50.8%, respectively. In the multivariate analysis of preoperative serum CEA levels >5 ng/mL, the prognostic factors for the OS and the DFS were the cutoff value ($P < 0.0001$) and the pN stage ($P < 0.0001$). CONCLUSION: A rate of decrease of more than 50% in the perioperative serum CEA level, as well as the normalization of the postoperative serum CEA level, may be useful factors for determining a prognosis for colon cancer patients with high preoperative CEA levels.

[862]

TÍTULO / TITLE: - A novel report of apoptosis in human lung carcinoma cells using selective agonist of d2-like dopamine receptors: a new approach for the treatment of human non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Immunopathol Pharmacol. 2013 Apr-Jun;26(2):393-402.

AUTORES / AUTHORS: - Sheikhpour M; Ahangari G; Sadeghizadeh M; Deezagi A
INSTITUCIÓN / INSTITUTION: - Department of Genetic, Faculty of Biological Sciences, Tarbiat Modares University, Tehran, Iran.

RESUMEN / SUMMARY: - In our previous study, a relationship between low expression of D2-like dopamine receptor genes and non-small cell lung cancer (NSCLC) disease was found. In this new research, by using selective agonist of these receptors, Bromocriptine (BR), we attempted to activate D2-like expression and apoptotic induction in a selective cell line of NSCLC. In addition, the relationship of apoptotic response of human lung carcinoma cells to BR and D2- dopamine receptor genes is investigated. Human lung cancer (QU-DB) cells were treated by five doses of BR at 48 h and cell viability was determined by MTT assay. The gene expression pattern of D2-like dopamine receptor Genes was studied by Real Time PCR. Nuclear morphology of cells was monitored by DAPI florescent staining then induction of DNA fragmentation by BR was shown in an agarose gel. Finally, the detection and quantification of apoptosis and its differentiation from necrosis was carried out by using Annexin-V-Fluos Staining. In this study, it is demonstrated that BR inhibited the proliferation of human lung cancer cells and induced apoptosis in them. In addition, the probable relationship between D2-dopamine receptor genes expression and the development of apoptosis was found. In conclusion, BR is responsible for induction of apoptosis in human lung cancer cells and can be used in treatment of these tumoric cells. In addition, normal expression of D2 dopamine receptors was associated with apoptotic effect of BR on these cells.

[863]

TÍTULO / TITLE: - Suppression of antifolate resistance by targeting the Myosin va trafficking pathway in melanoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Neoplasia. 2013 Jul;15(7):826-39.

AUTORES / AUTHORS: - Fernandez-Perez MP; Montenegro MF; Saez-Ayala M; Sanchez-Del-Campo L; Pinero-Madrona A; Cabezas-Herrera J; Rodriguez-Lopez JN

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology A, School of Biology, Regional Campus of International Excellence "Campus Mare Nostrum", University of Murcia, Murcia, España.

RESUMEN / SUMMARY: - Human melanoma is a significant clinical problem. As most melanoma patients relapse with lethal drug-resistant disease, understanding and preventing mechanism(s) of resistance is one of the highest priorities to improve melanoma therapy. Melanosomal sequestration and the cellular exportation of cytotoxic drugs have been proposed to be important melanoma-specific mechanisms that contribute to multidrug resistance in melanoma. Concretely, we found that treatment of melanoma with methotrexate (MTX) altered melanogenesis and accelerated the exportation of melanosomes; however, the cellular and molecular processes by which MTX is trapped into melanosomes and exported out of cells have not been elucidated. In this study, we identified myosin Va (MyoVa) as a possible mediator of these cellular processes. The results demonstrated that melanoma treatment with MTX leads to Akt2-dependent MyoVa phosphorylation, which enhances its ability to interact with melanosomes and accelerates their exportation. To understand the mechanism(s) by which MTX activates Akt2, we examined the effects of this drug on the activity of protein phosphatase 2^a, an Akt inhibitor activated by the methylation of its catalytic subunit. Taken together, this study identified a novel trafficking pathway in melanoma that promotes tumor resistance through Akt2/MyoVa activation. Because of these findings, we explored several MTX combination therapies to increase the susceptibility of melanoma to this drug. By avoiding MTX exportation, we observed that the E2F1 apoptotic pathway is functional in melanoma, and its induction activates p73 and apoptosis protease-activating factor 1 following a p53-autonomous proapoptotic signaling event.

[864]

TÍTULO / TITLE: - Peripheral blood derived gene panels predict response to infliximab in rheumatoid arthritis and Crohn's disease.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Genome Med. 2013 Jun 28;5(6):59.

●● [Enlace al texto completo \(gratis o de pago\) 1186/gm463](#)

AUTORES / AUTHORS: - Mesko B; Poliska S; Vancsa A; Szekanecz Z; Palatka K; Hollo Z; Horvath A; Steiner L; Zahuczky G; Podani J; Nagy AL

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Debrecen, Egyetemter, 4028, Hungary. nagyl@med.unideb.hu.

RESUMEN / SUMMARY: - BACKGROUND: Biological therapies have been introduced for the treatment of chronic inflammatory diseases including

rheumatoid arthritis (RA) and Crohn's disease (CD). The efficacy of biologics differs from patient to patient. Moreover these therapies are rather expensive, therefore treatment of primary non-responders should be avoided. **METHOD:** We addressed this issue by combining gene expression profiling and biostatistical approaches. We performed peripheral blood global gene expression profiling in order to filter the genome for target genes in cohorts of 20 CD and 19 RA patients. Then RT-quantitative PCR validation was performed, followed by multivariate analyses of genes in independent cohorts of 20 CD and 15 RA patients, in order to identify sets of interrelated genes that can separate responders from non-responders to the humanized chimeric anti-TNFalpha antibody infliximab at baseline. **RESULTS:** Gene panels separating responders from non-responders were identified using leave-one-out cross-validation test, and a pool of genes that should be tested on larger cohorts was created in both conditions. **CONCLUSIONS:** Our data show that peripheral blood gene expression profiles are suitable for determining gene panels with high discriminatory power to differentiate responders from non-responders in infliximab therapy at baseline in CD and RA, which could be cross-validated successfully. Biostatistical analysis of peripheral blood gene expression data leads to the identification of gene panels that can help predict responsiveness of therapy and support the clinical decision-making process.

[865]

TÍTULO / TITLE: - Apoptotic induction of skin cancer cell death by plant extracts.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Med Assoc Thai. 2013 Jan;96 Suppl 1:S60-4.

AUTORES / AUTHORS: - Thuncharoen W; Chulasiri M; Nilwarangkoon S; Nakamura Y; Watanapokasin R

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand.

RESUMEN / SUMMARY: - **OBJECTIVE:** The aim of the present study was to investigate the effects of plant extracts on cancer apoptotic induction. **MATERIAL AND METHOD:** Human epidermoid carcinoma A431 cell line, obtained from the American Type Culture Collection (ATCC, Manassas, VA), was maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) at 37 degrees C, 5% carbon dioxide (CO₂). Plant extract solutions were obtained from S & J international enterprises public company limited. These plant extracts include 50% hydroglycol extracts from *Etlingera elatior* (Jack) R.M.Smith (torch ginger; EE), *Rosa damascene* (damask rose; DR) and *Rafflesia kerrii* Meijer (bua phut; RM). The cell viability, time and dose dependency were determined by MTT (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay. A431 cells were treated with the plant extracts and stained with Hoechst 33342 fluorescent staining dye. **RESULTS:** Cell viability was demonstrated by the inhibitory concentration 50% (IC₅₀). The anti-proliferative effects were shown to be dependent on time and

dose. Typical characteristics of apoptosis which are cell morphological changes and chromatin condensation were clearly observed. CONCLUSION: The plant extracts was shown to be effective for anti-proliferation and induction of apoptosis cell death in skin cancer cells. Therefore, mechanisms underlying the cell death and its potential use for treatment of skin cancer will be further studied.

[866]

TÍTULO / TITLE: - A phase I study of three different dosing schedules of the oral aurora kinase inhibitor MSC1992371A in patients with solid tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Target Oncol. 2013 Jul 6.

●● Enlace al texto completo (gratis o de pago) [1007/s11523-013-0288-](http://1007/s11523-013-0288-3)

[3](#)

AUTORES / AUTHORS: - Mita M; Gordon M; Rejeb N; Gianella-Borradori A; Jago V; Mita A; Sarantopoulos J; Sankhala K; Mendelson D

INSTITUCIÓN / INSTITUTION: - Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, TX, USA, Monica.Mita@cshs.org.

RESUMEN / SUMMARY: - Aurora kinase inhibitors (AKIs) are a class of antimitotic, small-molecule anticancer agents. MSC1992371A is an AKI being evaluated for the treatment of patients with solid tumors. This phase I, open-label, dose-escalation study determined the maximum tolerated dose (MTD) of MSC1992371A in different dosing schedules in patients with locally advanced or metastatic solid tumors. MSC1992371A was administered on days 1 and 8 (schedule 1) or on days 1, 2, and 3 (schedule 2) of a 21-day cycle. The study was expanded with a third schedule (study drug on days 1-3 and 8-10). Adverse events were monitored throughout the study. Antitumor efficacy, drug pharmacokinetics, and pharmacodynamics were evaluated. Ninety-two patients were enrolled. MSC1992371A was dosed over eight levels in schedules 1 and 2, and the MTD was determined as 74 mg/m² per cycle for both schedules and as 60 mg/m² in schedule 3, albeit only in three patients due to discontinuation of the study. Overall, the most common grade 3 or 4 treatment-emergent adverse events were neutropenia, febrile neutropenia, thrombocytopenia, anemia, and fatigue. The most frequent dose-limiting toxicity over all schedules was neutropenia. MSC1992371A plasma concentrations tended to increase with increasing dose levels. Although no complete or partial responses were seen, stable disease \geq 3 months was observed in 11 patients. Analysis for markers of target modulation and pharmacodynamics effects was unsuccessful. MSC1992371A was generally well tolerated in patients, with mainly transient hematologic toxicities apparent at an MTD of 60-74 mg/m²/21-day cycle, independent of dosing frequency.

[867]

TÍTULO / TITLE: - Determination of the apoptotic index in osteosarcoma tissue and its relationship with patients prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Jun 4;13(1):56. doi: 10.1186/1475-2867-13-56.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-56](#)

AUTORES / AUTHORS: - Wu X; Cheng B; Cai ZD; Lou LM

INSTITUCIÓN / INSTITUTION: - Department of Orthopaedics, Shanghai tenth People's Hospital, Tongji University School of Medicine, No,301 Middle Yanchang Road, Shanghai, 200072, China. doctorwx@hotmail.com.

RESUMEN / SUMMARY: - BACKGROUND: Nowadays it remains a controversial issue whether a correlation exists between the apoptosis rate of tumor tissue and the prognosis of the patients. We aimed to explore the prognostic significance of apoptosis index of human osteosarcoma tissue. METHODS: The technique of terminal DNA breakpoints in situ 3 - hydroxy end labeling (TUNEL) was used to detect and analysis apoptosis index in 56 osteosarcoma specimens. The relationships between apoptosis index of tumor tissue and long term survival of patients as well as pathologic classification, tumor clinical stages, tumor size and level of serum alkaline phosphatase were analyzed. RESULTS: Our studies showed the cases with high apoptosis index had significantly longer survival time. Apoptosis index in osteosarcoma tissue was correlated with tumor size and level of serum alkaline phosphatase but not with pathologic classifications and clinical stages of tumor. CONCLUSION: Our results demonstrated that apoptosis index of osteosarcoma tissue combined with serum alkaline phosphatase could used as valid indicators to predicate the malignant level and prognosis of osteosarcoma cases, which would contribute to enhance efficacy of clinical treatments for osteosarcoma.

[868]

TÍTULO / TITLE: - Collaborative overexpression of matrix metalloproteinase-1 and vascular endothelial growth factor-C predicts adverse prognosis in patients with gliomas.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Epidemiol. 2013 Jul 16. pii: S1877-7821(13)00105-7. doi: 10.1016/j.canep.2013.06.006.

●● Enlace al texto completo (gratis o de pago)

[1016/j.canep.2013.06.006](#)

AUTORES / AUTHORS: - Xu Y; Zhong Z; Yuan J; Zhang Z; Wei Q; Song W; Chen H

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, First Affiliated Hospital of Medical College, Shantou University, Shantou City, Guangdong Province 515041, China. Electronic address: xuym777@163.com.

RESUMEN / SUMMARY: - Background and aim: Matrix metalloproteinase-1 (MMP-1), a member of the MMP family of zinc-dependent endopeptidases, has been

detected to be strongly expressed in gliomas with high tumor grade and to be correlated with increased tumor invasiveness. Vascular endothelial growth factor-C (VEGF-C), which is able to induce MMP-1 transcription, has been found to be upregulated in glioblastoma compared to low grade gliomas and non-neoplastic brain. The aim of the present study was to investigate the clinical significance of the co-expression of MMP-1 and VEGF-C in glioma patients on determining the prognosis. Methods: One hundred and sixteen glioma patients (26 World Health Organization (WHO) grade I, 30 WHO grade II, 30 WHO grade III, and 30 WHO grade IV) and 15 non-neoplastic brain specimens acquired from 15 patients undergoing surgery for epilepsy as control were collected. Immunohistochemistry was used to evaluate the expression of MMP-1 and VEGF-C in glioma and non-neoplastic brain tissues. The correlations of collaborative MMP-1 and VEGF-C expression with selected clinicopathologic parameters and clinical outcome of glioma patients were also assessed. Results: Both MMP-1 and VEGF-C expression were significantly higher in glioma tissues compared to non-neoplastic brain tissues (both $P < 0.001$). Of 116 glioma patients, 68 (58.62%) overexpressed MMP-1 and VEGF-C simultaneously. In addition, combined MMP-1 and VEGF-C expression was significantly associated with WHO grade ($P < 0.001$) and Karnofsky performance status (KPS) score ($P = 0.01$). Moreover, glioma patients expressing both MMP-1 and VEGF-C exhibited markedly poorer overall survival ($P < 0.001$). According to the multivariate analyses, collaborative overexpression of MMP-1 and VEGF-C was found to be an independent prognostic factor for overall survival ($P = 0.009$). Conclusions: Our data demonstrated for the first time that overexpression of both MMP-1 and VEGF-C may be an independent poor prognostic factor in gliomas, suggesting the interaction between MMP-1 and VEGF-C collaboratively stimulated advanced tumor progression and adverse outcome. Inhibiting both MMP-1 and VEGF-C could be a novel therapeutic approach for gliomas.

[869]

TÍTULO / TITLE: - Curcumin and Silibinin Inhibit Telomerase Expression in T47D Human Breast Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(6):3449-53.

AUTORES / AUTHORS: - Nasiri M; Zarghami N; Koshki KN; Mollazadeh M; Moghaddam MP; Yamchi MR; Esfahlan RJ; Barkhordari A; Alibakhshi A

INSTITUCIÓN / INSTITUTION: - Tuberculosis and Lung Research Center, Tabriz University of Medical Sciences, Tabriz, Iran E-mail : zarghami@tbzmed.ac.ir, zarghamin@yahoo.com.

RESUMEN / SUMMARY: - Background: Telomerase has been considered as an attractive molecular target for breast cancer therapy. The main objective of this work is to assess the inhibitory effects of silibinin and curcumin, two herbal substances, on telomerase gene expression in breast cancer cells. Materials

and Methods: For determination of cell viability tetrazolium-based assays were conducted after 24, 48, and 72 h exposure times and expression of human telomerase reverse transcriptase gene was measured with real-time PCR. Results: Each compound exerted cytotoxic effects on T47D cells and inhibited telomerase gene expression, both in a time-and dose-dependent manner. The mixture of curcumin and silibinin showed relatively more inhibitory effect on growth of T47D cells and hTERT gene expression as compared with either agent alone. Conclusions: These findings suggest that cell viability along with hTERT gene expression in breast cancer cells could be reduced by curcumin and silibinin.

[870]

TÍTULO / TITLE: - High Cytoplasmic Expression of the Orphan Nuclear Receptor NR4A2 Predicts Poor Survival in Nasopharyngeal Carcinoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(5):2805-9.

AUTORES / AUTHORS: - Wang J; Yang J; Li BB; He ZW

INSTITUCIÓN / INSTITUTION: - Sino-American Cancer Research Institute, Key Laboratory for Medical Molecular Diagnostics of Guangdong Province, Guangdong Medical College, Dongguan, China E-mail : zhiweihe66832@yahoo.cn.

RESUMEN / SUMMARY: - Objective: This study aimed at investigating whether the orphan nuclear receptor NR4A2 is significantly associated with clinicopathologic features and overall survival of patients with nasopharyngeal carcinoma (NPC). Methods: Immunohistochemistry was performed to determine NR4A2 protein expression in 84 NPC tissues and 20 non-cancerous nasopharyngeal (NP) tissues. The prognostic significance of NR4A2 protein expression was evaluated using Cox proportional hazards regression models and Kaplan-Meier survival analysis. Results: We did not find a significant association between total NR4A2 expression and clinicopathological variables in 84 patients with NPC. However, we observed that high cytoplasmic expression of NR4A2 was significantly associated with tumor size (T classification) (P = 0.006), lymph node metastasis (N classification) (P = 0.002) and clinical stage (P = 0.017). Patients with higher cytoplasmic NR4A2 expression had a significantly lower survival rate than those with lower cytoplasmic NR4A2 expression (P = 0.004). Multivariate Cox regression analysis suggested that the level of cytoplasmic NR4A2 expression was an independent prognostic indicator for overall survival of patients with NPC (P = 0.033). Conclusions: High cytoplasmic expression of NR4A2 is a potential unfavorable prognostic factor for patients with NPC.

[871]

TÍTULO / TITLE: - Serum tissue inhibitor of metalloproteinase 1 (TIMP-1) and vascular endothelial growth factor A (VEGF-A) are associated with prognosis in esophageal cancer patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Adv Med Sci. 2013 Jun 18:1-8. doi: 10.2478/ams-2013-0017.

●● Enlace al texto completo (gratis o de pago) [2478/ams-2013-0017](#)

AUTORES / AUTHORS: - Kozłowski M; Laudanski W; Mroczko B; Szmitkowski M; Milewski R; Lapuc G

RESUMEN / SUMMARY: - ABSTRACT Purpose: The matrix metalloproteinases, tissue inhibitors of metalloproteinases and angiogenesis contribute to growth and spread of cancer. We investigated the correlation between pretreatment serum levels of tissue inhibitor of metalloproteinase 1 (TIMP-1) and vascular endothelial growth factor A (VEGF-A), and clinicopathologic features and survival in patients with esophageal cancer (EC). Material/Methods: Serum TIMP-1 and VEGF-A were measured by enzyme-linked immunosorbent assay (ELISA) in 89 patients with EC, and 30 healthy controls. Results: Serum TIMP-1 and VEGF-A levels were significantly higher in patients with esophageal carcinoma than in the control group ($p=0.001$ and $p<0.001$, respectively). High levels of TIMP-1 were associated with histological type ($p<0.001$), tumor depth ($p<0.001$), stage ($p<0.001$) and lymph node metastases ($p=0.001$). Subgroup analysis showed that tumor size ($p<0.001$), tumor depth ($p<0.001$), stage ($p<0.001$), lymph node metastases ($p=0.002$), distant metastases ($p=0.009$) and resectability ($p=0.003$), were correlated with an elevated level of VEGF-A. Patients with elevated levels of TIMP-1 and VEGF-A had a significantly lower overall survival ($p=0.02$ and $p=0.048$, respectively), and disease-free survival (TIMP-1, $p<0.001$). Conclusion: High serum levels of TIMP-1 and VEGF-A were found to be associated with tumor progression and unfavorable prognosis in patients with EC.

[872]

TÍTULO / TITLE: - Effect of Bcl-2 on apoptosis and transcription factor NF-kappaB activation induced by adriamycin in bladder carcinoma BIU87 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(4):2387-91.

AUTORES / AUTHORS: - Zhang GJ; Zhang Z

INSTITUCIÓN / INSTITUTION: - Department of Hematology, Shengjing Hospital of China Medical University, Shenyang, China. zhanggj@sj-hospital.org

RESUMEN / SUMMARY: - Resistance to apoptosis is a major obstacle preventing effective therapy for malignancies. Bcl-2 plays a significant role in inhibiting apoptosis. We reconstructed a stable human Bcl-2 transfected cell line, BIU87-Bcl-2, that was derived from the transfection of human bladder carcinoma cell line BIU87 with a plasmid vector containing recombinant Bcl-2 [pcDNA3.1(+)-Bcl-2]. A cell line transfected with the plasmid alone [pcDNA3.1(+)-neo] was

also established as a control. BIU87 and BIU87-neo proved sensitive to adriamycin induced apoptosis, while BIU87-Bcl-2 was more resistant. In view of the growing evidence that NF-kappaB may play an important role in regulating apoptosis, we determined whether Bcl-2 could modulate the activity of NF-kappaB in bladder carcinoma cells. Stimulation of BIU87, BIU87-neo and BIU87-Bcl-2 with ADR resulted in an increase expression of NF-kappaB ($p < 0.001$). The expression of NF-kappaB in BIU87-Bcl-2 was higher than in the other two cases, with a concomitant reduction in the I kappa B kappa? protein level. These results suggest that the overexpression of Bcl-2 renders human bladder carcinoma cells resistant to adriamycin -induced cytotoxicity and there is a link between Bcl-2 and the NF-kappaB signaling pathway in the suppression of apoptosis.

[873]

TÍTULO / TITLE: - Epstein Barr virus DNA analysis in blood predicts disease progression in a rare case of plasmablastic lymphoma with effusion.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Infect Agent Cancer. 2013 Jul 23;8(1):28. doi: 10.1186/1750-9378-8-28.

●● Enlace al texto completo (gratis o de pago) [1186/1750-9378-8-28](#)

AUTORES / AUTHORS: - Friis A; Akerlund B; Christensson B; Gyllensten K; Aleman A; Zou JZ; Ernberg I

INSTITUCIÓN / INSTITUTION: - Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, SE-171 77 Stockholm, Sweden.

ingemar.ernberg@ki.se.

RESUMEN / SUMMARY: - BACKGROUND: In HIV-1-infected patients a long lasting CD4+ cell decline influences the host-EBV balance and thereby increases the risk for EBV related malignancies. In spite of a world-wide access to combination antiretroviral therapy (cART) there are still a considerable number of HIV-1-infected patients who will develop severe immunodeficiency. These undiagnosed HIV-1 infected patients, so called late testers, demonstrate an increased lymphoma risk, compared to patients diagnosed early. Consecutive individual screening for EBV DNA-load in late testers might be a useful predictor of emerging EBV-malignancy. METHODS: Patient biopsies and ascites were analyzed morphologically, by immunocyto-histochemistry and in-situ hybridization. Viral DNA and RNA load were quantified by PCR. Cell lines from primary tumor and from ascites, were established in vitro and further analyzed. RESULT: We here report on a case of EBV-positive lymphoma in an AIDS patient, first presenting with pleural effusion and ascites and was thus initially considered a primary effusion lymphoma (PEL) but was later diagnosed as a plasmablastic lymphoma (PBL). The patient had responded to cART with undetectable HIV-RNA and increased CD4 cell count one year prior to lymphoma presentation. At the time of lymphoma diagnosis the HIV-RNA

values were <50 RNA-copies per mL blood (undetectable) and the CD4-positive cell count 170 x10⁶/L. The lymphoma was CD45-negative and weakly CD22- and CD30-positive. The patient had a history of Kaposi sarcoma and HHV-8 seropositivity. The lymphoma biopsies, and three cell lines derived on different occasions from the tumor cell effusion, were all EBV-positive but HHV-8 negative. A noticeable EBV-DNA load decline was observed during the remission of the lymphoma following CHOP-therapy. The EBV-DNA load increased dramatically at the time of recurrence. CONCLUSION: EBV DNA load might be useful in monitoring the effect of lymphoma treatment as well as in estimating the risk of EBV-associated lymphoma in HIV-1 infected patients with pronounced immunosuppression.

[874]

TÍTULO / TITLE: - Development of new estrogen receptor-targeting therapeutic agents for tamoxifen-resistant breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Future Med Chem. 2013 Jun;5(9):1023-35. doi: 10.4155/fmc.13.63.

●● Enlace al texto completo (gratis o de pago) [4155/fmc.13.63](#)

AUTORES / AUTHORS: - Jiang Q; Zheng S; Wang G

INSTITUCIÓN / INSTITUTION: - Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70125, USA.

RESUMEN / SUMMARY: - Despite our deepening understanding of the mechanisms of resistance and intensive efforts to develop therapeutic solutions to combat resistance, de novo and acquired tamoxifen resistance remains a clinical challenge, and few effective regimens exist to treat tamoxifen-resistant breast cancer. The complexity of tamoxifen resistance calls for diverse therapeutic approaches. This review presents several therapeutic strategies and lead compounds targeting the estrogen receptor signaling pathways for treatment of tamoxifen-resistant breast cancer, with a critical assessment of challenges and potentials regarding clinical outcome. Medicinal chemistry holds the key to effective, personalized combination therapy for tamoxifen-resistant breast cancer by making available a diverse arsenal of small-molecule drugs that specifically target signaling pathways modulating hormone resistance. These combination therapy candidates should have the desired specificity, selectivity and low toxicity to resensitize tumor response to tamoxifen and/or inhibit the growth and proliferation of resistant breast cancer cells.

[875]

TÍTULO / TITLE: - Prognostic potential of ERCC1 protein expression and clinicopathologic factors in stage III/N2 non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cardiothorac Surg. 2013 Jun 10;8:149. doi: 10.1186/1749-8090-8-149.

●● Enlace al texto completo (gratis o de pago) [1186/1749-8090-8-149](https://doi.org/10.1371/journal.pone.0068798)

AUTORES / AUTHORS: - Yan D; Wei P; An G; Chen W

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Beijing Chao-Yang Hospital affiliated to Capital Medical University, Workers Stadium South Road, Beijing, China.

RESUMEN / SUMMARY: - BACKGROUND: Pathological stage III/N2 non-small cell lung cancer (NSCLC) is heterogeneous, and the optimal prognostic marker for survival remains unclear in Chinese patients. The aim of the present study was to assess the prognostic value of the clinicopathologic features and excision repair cross-complementing group-1 (ERCC1) in resected p-stage III/N2 NSCLC patients that received cisplatin-based adjuvant chemotherapy. METHODS: Clinical data concerning 115 patients with histopathologically confirmed stage III/N2 NSCLC who underwent a complete resection were reviewed retrospectively. All patients received cisplatin-based adjuvant chemotherapy. The protein expression levels for ERCC1 were immunohistochemically examined in 115 patients. The relationship between the ERCC1 protein expression level and the clinical outcomes of the patients was then observed. RESULTS: The 5-year survival rate and median survival time of patients with pathological stage III/N2 NSCLC after surgery and postoperative chemotherapy was 27.0% and 28.0 months, respectively. Survival of patients with ERCC1 negative tumors was significantly longer than those with ERCC1 positive tumors ($p = 0.004$). However, it was not entirely clear whether adjuvant chemotherapy with cisplatin-based agents was beneficial for ERCC1-negative patients with p-stage III/N2. A multivariate analysis of survival in patients with stage III/N2 NSCLC showed that surgical procedure (pneumonectomy vs. lobectomy; $p = 0.001$), number of involved lymph nodes (≤ 5 vs. >5 ; $p = 0.001$) and ERCC1 protein expression (negative vs. positive; $p = 0.012$) were significant prognostic factors. In addition, the prognosis of patients with skip mediastinal lymph node metastasis showed a tendency for improved survival, but this was not significant ($p = 0.432$). CONCLUSIONS: Findings from this retrospective study suggested that the number of involved lymph nodes and the type of pulmonary resection are significant and independent prognosis factors in patients with p-stage III/N2 NSCLC. In addition, it was found that ERCC1 protein expression might play an important role in the prognosis of p-stage III/N2 NSCLC patients treated with cisplatin-based adjuvant chemotherapy.

[876]

TÍTULO / TITLE: - Indications of clinical and genetic predictors for aromatase inhibitors related musculoskeletal adverse events in Chinese Han women with breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 19;8(7):e68798. doi: 10.1371/journal.pone.0068798. Print 2013 Jul 22.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0068798](https://doi.org/10.1371/journal.pone.0068798)

AUTORES / AUTHORS: - Wang J; Lu K; Song Y; Xie L; Zhao S; Wang Y; Sun W; Liu L; Zhao H; Tang D; Ma W; Pan B; Xuan Q; Liu H; Zhang Q

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, The Third Affiliated Hospital of Harbin Medical University, Harbin, China.

RESUMEN / SUMMARY: - BACKGROUND: Women with breast cancer treated with aromatase inhibitors (AIs) may experience musculoskeletal symptoms that lead to discontinuation of effective therapy. The purpose of the current study is to evaluate the clinical and genetic predictors for AIs-related musculoskeletal adverse events (MS-AEs). METHODOLOGY AND PRINCIPAL FINDINGS: We recruited 436 postmenopausal Chinese Han women receiving adjuvant AI therapy for early-stage hormone-sensitive breast cancer. Patients completed a self-administered questionnaire assessing the presence of musculoskeletal symptoms that started or worsened after initiating AIs. 27 single nucleotide polymorphisms (SNP) of ESR1, ESR2 and PGR were analyzed by Sequenom MassARRAY assays and /or PCR-based TaqMan assays. Of the 436 enrolled women, 206 cases experienced musculoskeletal symptoms. Patients who received taxane chemotherapy were more than two times more likely than other patients to have AIs-related MS-AEs. Genetic assay had showed that only two ESR1 SNPs, rs2234693 and rs9340799 were associated with AIs-related MS-AEs. TT genotype and the T allele in rs2234693 was statistically significantly lower in AIs-Related MS-AEs group than controls ($P = 0.001$; $P = 9.49E-7$). The frequency of AA genotype and the A allele in rs9340799 was higher ($P = 2.20E-5$; $P = 3.09E-4$). CONCLUSIONS AND SIGNIFICANCE: Our results suggested that prior taxane-based chemotherapy was the clinical predictor, while rs2234693 and rs9340799 were the genetic predictors for AIs-related MS-AEs.

[877]

TÍTULO / TITLE: - Testosterone induced apoptosis in colon cancer cells is regulated by PI3K/Rac1 signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian J Androl. 2013 Jun 17. doi: 10.1038/aja.2013.68.

- Enlace al texto completo (gratis o de pago) [1038/aja.2013.68](https://doi.org/10.1038/aja.2013.68)

AUTORES / AUTHORS: - Alkahtani S

RESUMEN / SUMMARY: - Recently, it has been reported that testosterone membrane signaling regulates actin reorganization and induces pro-apoptotic responses in colon tumor cells. In the present study the membrane androgen receptors (mARs)-induced activation of Rac1 GTPase and the involvement of PI3K/Rac1 signaling in controlling the apoptotic responses in testosterone treated Caco2 colon cancer cells has been analyzed. In line with previous findings, activation of mAR by testosterone conjugates triggered early and transient actin reorganization as indicated by the significant decrease of the G/Total actin ratio after 15- and 30-min treatment of the cells. Interestingly,

stimulation of mAR rapidly activated the Rac1 GTPase. This effect was evident after 15 min and persisted for at least 24 h. Testosterone induced Rac1 activation was fully blocked in Caco2 cells pre-treated with the PI3K inhibitor wortmannin, indicating that Rac1 signaling is acting downstream of the PI3K pathway. Remarkably, when cells were pre-treated with wortmannin that blocks the PI3K/Rac1 signaling, apoptotic response was almost fully inhibited. These findings suggest that Rac1 activation, triggering actin redistribution, is involved in testosterone induced pro-apoptotic responses governed by mAR activation and emphasize the regulatory role of PI3K/Rac1 signaling in colon tumors. Asian Journal of Andrology advance online publication, 17 June 2013; doi:10.1038/aja.2013.68.

[878]

TÍTULO / TITLE: - Aggressive Behavior and Elevated Lactate Dehydrogenase at Baseline Confer Inferior Prognosis in Patients With Primary Cutaneous Lymphoma.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lymphoma Myeloma Leuk. 2013 Jun 10. pii: S2152-2650(13)00149-3. doi: 10.1016/j.clml.2013.04.011.

●● Enlace al texto completo (gratis o de pago) 1016/j.clml.2013.04.011

AUTORES / AUTHORS: - Liu WP; Song YQ; Zheng W; Wang XP; Ding N; Zhu J

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China.

RESUMEN / SUMMARY: - BACKGROUND: Primary cutaneous lymphoma (PCL) comprises a heterogeneous group of diseases in regard to clinical presentation, histologic appearance, and biological behavior. Its rare occurrence limits analysis of disease features and survival of patients. PATIENTS AND METHODS: All patients with PCL treated in our hospital during January 2006 to October 2012 were included in this retrospective study. Their histologic and clinical data were analyzed. The diagnosis of PCL and the evaluation of clinical behavior were based on the 2005 World Health Organization-European Organisation for Research and Treatment of Cancer (WHO-EORTC) classification. RESULTS: Fifty-four cases of PCL were included in the study. The median age was 52.5 years. Thirteen (24.1%) patients had B-cell lymphoma and 41 (75.9%) had T-cell lymphoma. Twenty-nine (53.7%) patients exhibited disease having indolent clinical behavior, 14 (25.9%) presented with B symptoms, and 16 (29.6%) had elevated lactate dehydrogenase (LDH) levels at baseline. Within a median follow-up of 47.8 months, the expected 5-year progression-free survival (PFS) rate and overall survival (OS) rate were 6% and 14%, respectively. Using multivariate analysis, aggressive behavior (hazard ratio [HR], 2.92; P = .01) and elevated LDH levels at baseline (HR, 2.88; P = .01) were identified as independent risk factors for PFS. In addition, aggressive

behavior (HR, 4.09; P = .01) and elevated LDH levels at baseline (HR, 3.69; P = .01) were also identified as independent risk factors for OS. CONCLUSION: The study data suggest that aggressive behavior and elevated LDH levels at baseline were predictive factors for poor PFS and OS, which supports the need for immediate treatment of those patients.

[879]

TÍTULO / TITLE: - Prediction of Acute Toxicity Grade ≥ 3 in Patients With Locally Advanced Non-Small-Cell Lung Cancer Receiving Intensity Modulated Radiotherapy and Concurrent Low-Dose Cisplatin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Lung Cancer. 2013 Jul 5. pii: S1525-7304(13)00067-3. doi: 10.1016/j.clcc.2013.04.001.

●● Enlace al texto completo (gratis o de pago) 1016/j.clcc.2013.04.001

AUTORES / AUTHORS: - Uyterlinde W; Belderbos J; Baas C; van Werkhoven E; Knegjens J; Baas P; Smit A; Rikers C; van den Heuvel M

INSTITUCIÓN / INSTITUTION: - Department of Thoracic Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands. Electronic address: w.uyterlinde@nki.nl.

RESUMEN / SUMMARY: - BACKGROUND: Intensity modulated radiotherapy (IMRT) is increasingly used with concurrent chemotherapy but toxicity data are not well investigated. We correlated clinical and dosimetric parameters with acute toxicity grade ≥ 3 in patients with locally advanced NSCLC treated with IMRT and concurrent low-dose cisplatin. PATIENTS AND METHODS: We analyzed age, PS, comorbidities, gross tumor volume, and the volume of the esophagus irradiated with 50 Gy (V50oes) in relation with acute toxicity. The mean lung dose (MLD) and pulmonary toxicity was described. Treatment consisted of 24 x 2, 75 Gy, and daily cisplatin 6 mg/m². Patients with an MLD ≥ 20 Gy or a PS > 2 were excluded from CCRT. Toxicity was prospectively scored using the Common Toxicity Criteria for adverse events version 3.0. The Charlson Comorbidity Index (CCI) was applied for scoring comorbidities. Multivariable logistic regressions for toxicity and survival estimates (Kaplan-Meier) were used for evaluation. RESULTS: From 2008 to 2011, 188 patients received standard CCRT. In 35% of the patients, acute toxicity grade ≥ 3 was reported. Grade 5 toxicity was scored in 1% of the patients. V50oes (odds ratio [OR], 1.33 per 10% increase; P = .01) and PS ≥ 2 (OR, 3.45; P = .07) were significantly correlated with acute toxicity ≥ 3 . No differences in toxicity were observed between age groups (< 70 and ≥ 70 ; P = .26), and those with a CCI score < 5 and ≥ 5 , and acute severe toxicity (P = .36). Grade ≥ 3 pulmonary toxicity was seen in 7%. The 1- and 2-year overall survival in stage III disease were 78% and 52%, respectively. Patients with a poor PS or a high CCI score had similar survival outcomes. CONCLUSION: Concurrent low-dose cisplatin using IMRT is effective in a large cohort of consecutive patients with

NSCLC and life threatening toxicity is rare (1%). PS \geq 2 and V50oes are correlated with acute toxicity grade \geq 3.

[880]

TÍTULO / TITLE: - Enhanced induction of cell cycle arrest and apoptosis via the mitochondrial membrane potential disruption in human U87 malignant glioma cells by aloe emodin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Asian Nat Prod Res. 2013 Jul 22.

●● Enlace al texto completo (gratis o de pago)

[1080/10286020.2013.818982](https://doi.org/10.1080/10286020.2013.818982)

AUTORES / AUTHORS: - Ismail S; Haris K; Abdul Ghani AR; Abdullah JM; Johan MF; Mohamed Yusoff AA

INSTITUCIÓN / INSTITUTION: - a Department of Neurosciences , Universiti Sains Malaysia , Kubang Kerian , Kelantan , 16150 , Malaysia.

RESUMEN / SUMMARY: - Aloe emodin, one of the active compounds found in Aloe vera leaves, plays an important role in the regulation of cell growth and death. It has been reported to promote the anti-cancer effects in various cancer cells by inducing apoptosis. However, the mechanism of inducing apoptosis by this agent is poorly understood in glioma cells. This research is to investigate the apoptosis and cell cycle arrest inducing by aloe emodin on U87 human malignant glioma cells. Aloe emodin showed a time- and dose-dependent inhibition of U87 cells proliferation and decreased the percentage of viable U87 cells via the induction of apoptosis. Characteristic morphological changes, such as the formation of apoptotic bodies, were observed with confocal microscope by Annexin V-FITC/PI staining, supporting our viability study and flow cytometry analysis results. Our data also demonstrated that aloe emodin arrested the cell cycle in the S phase and promoted the loss of mitochondrial membrane potential in U87 cells that indicated the early event of the mitochondria-induced apoptotic pathway.

[881]

TÍTULO / TITLE: - MicroRNA-497 Suppresses Proliferation and Induces Apoptosis in Prostate Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(6):3499-502.

AUTORES / AUTHORS: - Wang L; Li B; Li L; Wang T

INSTITUCIÓN / INSTITUTION: - Department of Urology, Affiliated Hospital of Hebei, University of Engineering, Handan, Hebei, China E-mail : liwanghebei@gmail.com.

RESUMEN / SUMMARY: - MicroRNAs (miRNAs) are a class of endogenously expressed small, non-coding, single-stranded RNAs that negatively regulate gene expression, mainly by binding to 3'- untranslated regions (3'UTR) of their

target messenger RNAs (mRNAs), which cause blocks of translation and/or mRNA cleavage. Recently, miRNA profiling studies demonstrated the microRNA-497 (miR-497) level to be down-regulated in all prostate carcinomas compared with BPH samples. The purpose of this study was to investigate the potential role of miR-497 in human prostate cancer. Proliferation, cell cycle and apoptosis assays were conducted to explore the potential function of miR-497 in human prostate cancer cells. Results showed that miR-497 suppressed cellular growth and initiated G0/G1 phase arrest of LNCaP and PC-3 cells. We also observed that miR-497 increased the percentage of apoptotic cells by increasing caspase-3/7 activity. Taken together, our results demonstrated that miR-497 can inhibit growth and induce apoptosis by caspase-3 activation in prostate cancer cells, which suggest its use as a potential therapeutic target in the future.

[882]

TÍTULO / TITLE: - Combining trail with p13 kinase or hsp90 inhibitors enhances apoptosis in colorectal cancer cells via suppression of survival signaling.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncotarget. 2013 Jul 14.

AUTORES / AUTHORS: - Saturno G; Valenti M; De Haven Brandon A; Thomas GV; Eccles S; Clarke PA; Workman P

INSTITUCIÓN / INSTITUTION: - Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, London, UK.

RESUMEN / SUMMARY: - TRAIL has been shown to induce apoptosis in cancer cells, but in some cases they fail to respond to this ligand. We explored the ability of representative phosphatidylinositol-3-kinase (PI3 Kinase)/mTOR and HSP90 inhibitors to overcome TRAIL resistance by increasing apoptosis in colorectal cancer models. We determined the sensitivity of 27 human colorectal cancer and 2 non-transformed colon epithelial cell lines to TRAIL treatment. A subset of the cancer cell lines with a range of responses to TRAIL was selected from the panel for treatment with TRAIL combined with the PI3 Kinase/mTOR inhibitor PI-103 or the HSP90 inhibitor 17-AAG (tanespimycin). Two TRAIL-resistant cell lines were selected for in vivo combination studies with TRAIL and 17-AAG. We found that 13 colorectal cancer cell lines and the 2 non-transformed colon epithelial cell lines were resistant to TRAIL. We demonstrated that co-treatment of TRAIL and PI-103 or 17-AAG was synergistic or additive and significantly enhanced apoptosis in colorectal cancer cells. This was associated with decreased expression or activity of survival protein biomarkers such as ERBB2, AKT, IKK α and XIAP. In contrast, the effect of the combination treatments in non-transformed colon cells was minimal. We show here for the first time that co-treatment in vivo with TRAIL and 17-AAG in two TRAIL-resistant human colorectal cancer xenograft models resulted in

significantly greater tumor growth inhibition compared to single treatments. We propose that combining TRAIL with PI3 Kinase/mTOR or HSP90 inhibitors has therapeutic potential in the treatment of TRAIL-resistant colorectal cancers.

[883]

TÍTULO / TITLE: - EGFR mutations detected on cytology samples by a centralized laboratory reliably predict response to gefitinib in non-small cell lung carcinoma patients.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cytopathol. 2013 Jun 18. doi: 10.1002/cncy.21322.

●● [Enlace al texto completo \(gratis o de pago\) 1002/cncy.21322](#)

AUTORES / AUTHORS: - Malapelle U; Bellevicine C; De Luca C; Salatiello M; De Stefano A; Rocco D; de Rosa N; Vitiello F; Russo S; Pepe F; Iaccarino A; Micheli P; Illiano A; Carlomagno C; Piantedosi FV; Troncone G

INSTITUCIÓN / INSTITUTION: - Department of Public Health, University of Naples Federico II, Naples, Italy.

RESUMEN / SUMMARY: - BACKGROUND: Epidermal growth factor receptor (EGFR) mutations are reliably detected by referral laboratories, even if most lung cancer cytology specimens sent to such laboratories contain very few cells. However, EGFR mutations may be distributed heterogeneously within tumors, thereby raising concerns that mutations detected on cytology are not representative of the entire tumor and, thus, are less reliable in predicting response to tyrosine kinase inhibitor (TKI) treatment than mutations detected on histology. To address this issue, the authors reviewed their clinical practice archives and compared the outcome of TKI treatment among patients who were selected by cytology versus patients who were selected by histology. METHODS: From July 2010 to July 2012, 364 cytology samples and 318 histology samples were received. Exon 19 deletions and the L858R point mutation in exon 21, detected by fragment assay and TaqMan assay, respectively, were confirmed by direct sequencing; discrepancies were resolved by cloning polymerase chain reaction products. The response rate (RR) and progression-free survival (PFS) at 12 months (range, 3-34 months) were evaluable in 13 EGFR-mutated patients who were selected for treatment by cytology and 13 patients who were selected by histology. RESULTS: The mutation rate was similar in histology samples (8.5%) and cytology samples (8.8%). The RR (54%) and PFS (9.2 months) were similar in histologically selected patients and cytologically selected patients (RR, 62%; PFS, 8.6 months; P = .88). The disease control rate (responsive plus stable disease) was 92% in histologically selected patients and 100% in cytologically selected patients. CONCLUSIONS: EGFR mutations detected on cytology specimens by a centralized laboratory can predict TKI treatment response equally well as mutations identified on histology samples. Cancer (Cancer Cytopathol) 2013. © 2013 American Cancer Society.

[884]

TÍTULO / TITLE: - Activation of Wnt/beta-Catenin Signaling Increases Apoptosis in Melanoma Cells Treated with Trail.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 15;8(7):e69593. doi: 10.1371/journal.pone.0069593. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0069593](https://doi.org/10.1371/journal.pone.0069593)

AUTORES / AUTHORS: - Zimmerman ZF; Kulikauskas RM; Bomsztyk K; Moon RT; Chien AJ

INSTITUCIÓN / INSTITUTION: - Department of Medicine, the University of Washington School of Medicine, Seattle, Washington, United States of America.

RESUMEN / SUMMARY: - While the TRAIL pathway represents a promising therapeutic target in melanoma, resistance to TRAIL-mediated apoptosis remains a barrier to its successful adoption. Since the Wnt/beta-catenin pathway has been implicated in facilitating melanoma cell apoptosis, we investigated the effect of Wnt/beta-catenin signaling on regulating the responses of melanoma cells to TRAIL. Co-treatment of melanoma cell lines with WNT3A-conditioned media and recombinant TRAIL significantly enhanced apoptosis compared to treatment with TRAIL alone. This apoptosis correlates with increased abundance of the pro-apoptotic proteins BCL2L11 and BBC3, and with decreased abundance of the anti-apoptotic regulator Mcl1. We then confirmed the involvement of the Wnt/beta-catenin signaling pathway by demonstrating that siRNA-mediated knockdown of an intracellular beta-catenin antagonist, AXIN1, or treating cells with an inhibitor of GSK-3 also enhanced melanoma cell sensitivity to TRAIL. These studies describe a novel regulation of TRAIL sensitivity in melanoma by Wnt/beta-catenin signaling, and suggest that strategies to enhance Wnt/beta-catenin signaling in combination with TRAIL agonists warrant further investigation.

[885]

TÍTULO / TITLE: - Identification of caveolin-1 as a potential causative factor in the generation of trastuzumab resistance in breast cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cancer. 2013 Jun 21;4(5):391-401. doi: 10.7150/jca.6470. Print 2013.

●● Enlace al texto completo (gratis o de pago) [7150/jca.6470](https://doi.org/10.7150/jca.6470)

AUTORES / AUTHORS: - Sekhar SC; Kasai T; Satoh A; Shigehiro T; Mizutani A; Murakami H; El-Aarag BY; Salomon DS; Massaguer A; de Llorens R; Seno M

INSTITUCIÓN / INSTITUTION: - 1. Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, Okayama 7008530, Japan.

RESUMEN / SUMMARY: - The oncogenic tyrosine kinase receptor ErbB2 is a prognostic factor and target for breast cancer therapeutics. In contrast with the other ErbB receptors, ErbB2 is hardly internalized by ligand induced mechanisms, indicating a prevalent surface expression. Elevated levels of ErbB2 in tumor cells are associated with its defective endocytosis and down regulation. Here we show that caveolin-1 expression in breast cancer derived SKBR-3 cells (SKBR-3/Cav-1) facilitates ligand induced ErbB2 endocytosis using an artificial peptide ligand EC-eGFP. Similarly, stimulation with humanized anti ErbB2 antibody Trastuzumab (Herceptin) was found to be internalized and co-localized with caveolin-1 in SKBR-3/Cav-1 cells. Internalized EC-eGFP and Trastuzumab in SKBR-3/Cav-1 cells were then delivered via caveolae to the caveolin-1 containing early endosomes. Consequently, attenuated Fc receptor mediated ADCC functions were observed when exposed to Trastuzumab and EC-Fc (EC-1 peptide conjugated to Fc part of human IgG). On the other hand, this caveolae dependent endocytic synergy was not observed in parental SKBR-3 cells. Therefore, caveolin-1 expression in breast cancer cells could be a predictive factor to estimate how cancer cells are likely to respond to Trastuzumab treatment.

[886]

TÍTULO / TITLE: - Predictive factors determining neoadjuvant chemotherapy outcomes in breast cancer - a single center experience.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(4):2401-6.

AUTORES / AUTHORS: - Yu Y; Xiang H; He XM; Yang HJ; Zong XY

INSTITUCIÓN / INSTITUTION: - Department of Breast Surgery, Zhejiang Cancer Hospital, China.

RESUMEN / SUMMARY: - From January 1, 2008 to March 31, 2010, 101 patients with stage II-III breast cancer were enrolled in this study and subjected to an anthracycline-based neoadjuvant chemotherapy regimen with or without docetaxel. Surgery was performed after 2-6 cycles of chemotherapy, and the clinical response was determined by pathological and histochemical assessments. The clinical response rate, as indicated by complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were 6.9, 52.5, 36.6, and 4.0%, respectively. A multivariable correlation analysis indicated that the overall clinical response rate correlated with the number of metastatic lymph nodes, number of chemotherapy cycles, and vessel invasion status. Importantly, the CR rate was only associated with the number of chemotherapy cycles. Nonparametric tests failed to detect a correlation between HER2 or Topo IIalpha status and clinical response to neoadjuvant chemotherapy in these patients. When they were stratified by HER2 or HR status, for HER2-positive patients the CR rate was associated with vessel invasion and Topo IIalpha status. Based on our findings, we propose that HR, HER-2 and Topo IIalpha are not putative predictive biomarkers of

chemotherapy outcome for breast cancer patients. Topo IIalpha expression level was only inversely correlated with CR rate among HR-positive patients. Importantly, the achievement of CR was largely related to the number of chemotherapy cycles.

[887]

TÍTULO / TITLE: - Germacrone induces apoptosis in human hepatoma HepG2 cells through inhibition of the JAK2/STAT3 signalling pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Huazhong Univ Sci Technolog Med Sci. 2013 Jun;33(3):339-45. doi: 10.1007/s11596-013-1121-z. Epub 2013 Jun 17.

●● Enlace al texto completo (gratis o de pago) [1007/s11596-013-1121-](#)

[z](#)

AUTORES / AUTHORS: - Liu YY; Zheng Q; Fang B; Wang W; Ma FY; Roshan S; Banafa A; Chen MJ; Chang JL; Deng XM; Li KX; Yang GX; He GY

INSTITUCIÓN / INSTITUTION: - The Genetic Engineering International Cooperation Base of Chinese Ministry of Science and Technology, Chinese National Center of Plant Gene Research (Wuhan) HUST Part, Key Laboratory of Molecular Biophysics of Chinese Ministry of Education, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan, 430074, China, liuyunyi1987@yahoo.com.cn.

RESUMEN / SUMMARY: - Previous studies have shown that STAT3 plays a vital role in the genesis and progression of cancer. In this study, we investigated the relationship between the JAK2/STAT3 signalling pathway and germacrone-induced apoptosis in HepG2 cells. HepG2 cells were incubated with germacrone for 24 h, the protein expression of p-STAT3, STAT3, p-JAK2 and JAK2 was detected by Western Blotting, and RT-PCR was used to determine the expression of STAT3, p53, Bcl-2 and Bax at transcriptional levels. Besides that, HepG2 cells were pre-treated with AG490 or IL-6 for 2 h, and then incubated with germacrone for 24 h. The expression of p-JAK2, JAK2, p-STAT3, STAT3, p53, Bax and Bcl-2 was detected by Western blotting. The activity of HepG2 cells was tested by MTT assay. The apoptosis of HepG2 cells and levels of reactive oxygen species (ROS) were flow cytometrically measured. The results showed that germacrone exposure decreased p-STAT3 and p-JAK2 and regulated expression of p53 and Bcl-2 family members at the same time. Moreover, IL-6 enhanced the activation of the JAK2/STAT3 signalling pathway and therefore attenuated the germacrone-induced apoptosis. Suppression of JAK2/STAT3 signalling pathway by AG490, an inhibitor of JAK2, resulted in apoptosis and an increase in ROS in response to germacrone exposure. We therefore conclude that germacrone induces apoptosis through the JAK2/STAT3 signalling pathway.

[888]

TÍTULO / TITLE: - 6,8-dihydroxy-7-methoxy-1-methyl-azafluorenone induces caspase-8- and -9-mediated apoptosis in human cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(4):2637-41.

AUTORES / AUTHORS: - Banjerdpongchai R; Khaw-On P; Ristee C; Pompimon W

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. ratana.b@cmu.ac.th

RESUMEN / SUMMARY: - 6,8-dihydroxy-7-methoxy-1-methyl-azafluorenone (DMMA), a purified compound from *Polyalthia cerasoides* roots, is cytotoxic to various cancer cell lines. The aims of this study were to demonstrate the type of cancer cell death and the mechanism(s) involved. DMMA inhibited cell growth and induced apoptotic death in human leukemic cells (HL-60, U937, MOLT-4), human breast cancer MDA-MB231 cells and human hepatocellular carcinoma HepG2 cells in a dose dependent manner, with IC50 values ranging between 20-55 μ M DMMA also decreased cell viability of human peripheral blood mononuclear cells. The morphology of cancer cells induced by the compound after staining with propidium iodide and examined under a fluorescence microscope was condensed nuclei and apoptotic bodies. Mitochondrial transmembrane potential (MTP) was decreased after 24h exposure in all five types of cancer cells. DMMA-induced caspase-3, -8, and -9 activity was strongly induced in human leukemic HL-60 and MOLT-4 cells, while in U937-, MDA-MB231- and HepG2-treated cells there was partial induction of caspase. In conclusion, DMMA-induced activation of caspase-8 and -9 resulted in execution of apoptotic cell death in human leukemic HL-60 and MOLT-4 cell lines via extrinsic and intrinsic pathways.

[889]

TÍTULO / TITLE: - Generation of reactive oxygen species by polyenylpyrroles derivatives causes DNA damage leading to G2/M arrest and apoptosis in human oral squamous cell carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 28;8(6):e67603. doi: 10.1371/journal.pone.0067603. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1371/journal.pone.0067603](https://doi.org/10.1371/journal.pone.0067603)

AUTORES / AUTHORS: - Hua KF; Liao PC; Fang Z; Yang FL; Yang YL; Chen YL; Chiu YC; Liu ML; Lam Y; Wu SH

INSTITUCIÓN / INSTITUTION: - Department of Biotechnology and Animal Science, National Ilan University, Ilan, Taiwan.

RESUMEN / SUMMARY: - Oral squamous cell carcinoma (OSCC) accounts for 5.8% of all malignancies in Taiwan and the incidence of OSCC is on the rise.

OSCC is also a common malignancy worldwide and the five-year survival rate remains poor. Therefore, new and effective treatments are needed to control OSCC. In the present study we have investigated the efficacy and associated mechanisms of polyenylpyrroles and their analogs in both in vitro cell culture and in vivo nude mice xenografts. Auxarconjugatin B (compound 1^a) resulted in cell cycle arrest in the G2/M phase and caspase-dependent apoptosis in OEC-M1 and HSC-3 cells by activating DNA damage and mitochondria dysfunction through the loss of mitochondrial membrane potential, release of cytochrome c, increase in B-cell lymphoma-2-associated X protein level, and decrease in B-cell lymphoma-2 level. Compound 1^a-induced generation of intracellular reactive oxygen species through cytochrome P450 1^{a1} was identified as a major mechanism of its effect for DNA damage, mitochondria dysfunction and apoptosis, which was reversed by antioxidant N-acetylcysteine as well as cytochrome P450 1^{a1} inhibitor and specific siRNA. Furthermore, compound 1^a-treated nude mice showed a reduction in the OEC-M1 xenograft tumor growth and an increase in the caspase-3 activation in xenograft tissue. These results provide promising insights as to how compound 1^a mediates cytotoxicity and may prove to be a molecular rationale for its translation into a potential therapeutic against OSCC.

[890]

TÍTULO / TITLE: - Cancer testis antigens and NY-BR-1 expression in primary breast cancer: prognostic and therapeutic implications.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jun 3;13:271. doi: 10.1186/1471-2407-13-271.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-271](#)

AUTORES / AUTHORS: - Balafoutas D; zur Hausen A; Mayer S; Hirschfeld M; Jaeger M; Denschlag D; Gitsch G; Jungbluth A; Stickeler E

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, University Hospital Freiburg, Freiburg 79106, Germany.

RESUMEN / SUMMARY: - BACKGROUND: Cancer-testis antigens (CTA) comprise a family of proteins, which are physiologically expressed in adult human tissues solely in testicular germ cells and occasionally placenta. However, CTA expression has been reported in various malignancies. CTAs have been identified by their ability to elicit autologous cellular and or serological immune responses, and are considered potential targets for cancer immunotherapy. The breast differentiation antigen NY-BR-1, expressed specifically in normal and malignant breast tissue, has also immunogenic properties. Here we evaluated the expression patterns of CTAs and NY-BR-1 in breast cancer in correlation to clinico-pathological parameters in order to determine their possible impact as prognostic factors. METHODS: The reactivity pattern of various mAbs (6C1, MA454, M3H67, 57B, E978, GAGE #26 and NY-BR-1 #5) were assessed by immunohistochemistry in a tissue micro array

series of 210 randomly selected primary invasive breast cancers in order to study the diversity of different CTAs (e.g. MAGE-A, NY-ESO-1, GAGE) and NY-BR-1. These expression data were correlated to clinico-pathological parameters and outcome data including disease-free and overall survival. RESULTS: Expression of at least one CTA was detectable in the cytoplasm of tumor cells in 37.2% of the cases. NY-BR-1 expression was found in 46.6% of tumors, respectively. Overall, CTA expression seemed to be linked to adverse prognosis and M3H67 immunoreactivity specifically was significantly correlated to shorter overall and disease-free survival ($p=0.000$ and 0.024 , respectively). CONCLUSIONS: Our findings suggest that M3H67 immunoreactivity could serve as potential prognostic marker in primary breast cancer patients. The exclusive expression of CTAs in tumor tissues as well as the frequent expression of NY-BR-1 could define new targets for specific breast cancer therapies.

[891]

TÍTULO / TITLE: - Induction of apoptosis associated with chromosomal DNA fragmentation and caspase-3 activation in leukemia L1210 cells by TiO nanoparticles.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biosci Bioeng. 2013 Jul 10. pii: S1389-1723(13)00222-3. doi: 10.1016/j.jbiosc.2013.06.003.

●● Enlace al texto completo (gratis o de pago)

[1016/j.jbiosc.2013.06.003](#)

AUTORES / AUTHORS: - Takaki K; Higuchi Y; Hashii M; Ogino C; Shimizu N

INSTITUCIÓN / INSTITUTION: - Division of Biological Measurement and Applications, Institute of Nature and Environmental Technology, Kanazawa University, Kanazawa 920-1192, Japan.

RESUMEN / SUMMARY: - We investigated the effects of nanosized TiO₂ particles on the death of mouse leukemia L1210 cells. TiO₂ particles suppressed proliferation and induced cell death, as measured by lactate dehydrogenase (LDH) release into the culture medium. Chromatin condensation, which is typical of the initiation of cell death, was observed in approximately 14% cells cultured with titanium dioxide (TiO₂) particles for 12 h. Furthermore, giant DNA fragments of approximately 2 Mbp and high-molecular-weight DNA fragments between 100 kbp and 1 Mbp were observed in cells cultured for 18 h with TiO₂ particles. These giant and high-molecular-weight DNA fragments were further degraded into smaller DNA fragments, appearing as DNA ladders. Corresponding to the generation of DNA fragments, caspase-3 activity increased in cells treated with TiO₂ particles. TiO₂ particle-induced LDH release was not inhibited by cytochalasin D, an inhibitor of endocytosis. These results suggest that nanosized TiO₂ particles can induce apoptosis associated with DNA fragmentation and caspase-3 activation and that TiO₂ particle-

induced apoptosis is not caused by endocytosis but is associated with contact of the particles with the cell surface.

[892]

TÍTULO / TITLE: - Towards predicting the response of a solid tumour to chemotherapy and radiotherapy treatments: clinical insights from a computational model.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS Comput Biol. 2013 Jul;9(7):e1003120. doi: 10.1371/journal.pcbi.1003120. Epub 2013 Jul 11.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pcbi.1003120](#)

AUTORES / AUTHORS: - Powathil GG; Adamson DJ; Chaplain MA

INSTITUCIÓN / INSTITUTION: - Division of Mathematics, University of Dundee, Dundee, United Kingdom.

RESUMEN / SUMMARY: - In this paper we use a hybrid multiscale mathematical model that incorporates both individual cell behaviour through the cell-cycle and the effects of the changing microenvironment through oxygen dynamics to study the multiple effects of radiation therapy. The oxygenation status of the cells is considered as one of the important prognostic markers for determining radiation therapy, as hypoxic cells are less radiosensitive. Another factor that critically affects radiation sensitivity is cell-cycle regulation. The effects of radiation therapy are included in the model using a modified linear quadratic model for the radiation damage, incorporating the effects of hypoxia and cell-cycle in determining the cell-cycle phase-specific radiosensitivity. Furthermore, after irradiation, an individual cell's cell-cycle dynamics are intrinsically modified through the activation of pathways responsible for repair mechanisms, often resulting in a delay/arrest in the cell-cycle. The model is then used to study various combinations of multiple doses of cell-cycle dependent chemotherapies and radiation therapy, as radiation may work better by the partial synchronisation of cells in the most radiosensitive phase of the cell-cycle. Moreover, using this multi-scale model, we investigate the optimum sequencing and scheduling of these multi-modality treatments, and the impact of internal and external heterogeneity on the spatio-temporal patterning of the distribution of tumour cells and their response to different treatment schedules.

[893]

TÍTULO / TITLE: - Inhibition by imatinib of expression of O-glycan-related glycosyltransferases and tumor-associated carbohydrate antigens in the K562 human leukemia cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(4):2447-51.

AUTORES / AUTHORS: - Sun QC; Liu MB; Shen HJ; Jiang Z; Xu L; Gao LP; Ni JL; Wu SL

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Medical College of Soochow University, Suzhou, Jiangsu, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To study changes of tumor associated carbohydrate antigen (TACAs) expression and mRNA levels for tumor associated glycosyltransferases, and assess subcellular localizations of N-acetyl galactosyltransferases (GalNAc-Ts) in the K562 leukemia cell line after imatinib treatment. **METHODS:** RT-PCR was performed to analyze the expression of glycosyltransferases which synthesize O-glycan in tumor-associated carbohydrate antigens (TCTAs). The expression of Tn antigen, T antigen and sialyl T antigen on K562 cell membranes was measured by flow cytometry after treatment with different concentrations of imatinib. Co-localization of GalNAc-Ts and ER (endoplasmic reticulum) was determined by confocal laser scanning microscopy. **RESULTS:** Transcript expression levels of several glycosyltransferases related to TCTAs were decreased after imatinib (0-0.3µM) treatment. Expression of Tn antigen and T antigen was increased while that of sialyl T antigen was decreased. Co-localization of GalNAc-Ts and ER was reduced by 0.2µM of imatinib. **CONCLUSION:** Imatinib inhibited the expression of O-glycan related TACAs and several related glycosyltransferases, while decreasing the co-localization of GalNAc-Ts and ER and normalizing O-glycosylation in the K562 human leukemia cell.

[894]

TÍTULO / TITLE: - Receptor-associated protein blocks internalization and cytotoxicity of myeloma light chain in cultured human proximal tubular cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 23;8(7):e70276. doi: 10.1371/journal.pone.0070276. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0070276

AUTORES / AUTHORS: - Sengul S; Erturk S; Khan AM; Batuman V

INSTITUCIÓN / INSTITUTION: - Department of Nephrology, Ankara University School of Medicine, Ankara, Turkey.

RESUMEN / SUMMARY: - **BACKGROUND:** Free light chains (LCs) are among the many ligands that bind to cubilin/megalin for endocytosis via the clathrin-dependent endosomal/lysosomal pathway. Receptor associated protein (RAP), is a 39 kDA high-affinity, chaperone-like ligand for megalin that assists in the proper folding and functioning of megalin/cubilin. Although RAP is known to inhibit ligand binding to megalin/cubilin, its effect on LC endocytosis has not been shown directly. **METHODS AND PRINCIPAL FINDINGS:** We investigated whether RAP can block the endocytosis of LC in cultured human proximal tubule cells and whether this can prevent LC cytotoxicity. Immunofluorescence microscopy and flow cytometry showed that fluorescently labeled LC endocytosis was markedly inhibited in HK-2 cells pretreated with human RAP.

The effect of RAP was dose-dependent, and was predominantly on endocytosis as it had no effect on the small acid-washable fraction of LC bound to cell membrane. RAP significantly inhibited LC induced cytokine production and phosphorylation of ERK1/2 and p38 MAPK. Prolonged exposure to LC for 48 h resulted in epithelial-to-mesenchymal transformation in HK-2 cells as evidenced by marked reduction in the expression of the epithelial cell marker E-cadherin, and increased the expression of the mesenchymal marker alpha-SMA, which was also prevented by RAP in the endocytosis medium. CONCLUSIONS: RAP inhibited LC endocytosis by approximately 88% and ameliorated LC-induced cytokine responses and EMT in human PTCs. The results not only provide additional evidence that LCs endocytosis occurs via the megalin/cubilin endocytic receptor system, but also show that blocking LC endocytosis by RAP can protect proximal tubule cells from LC cytotoxicity.

[895]

TÍTULO / TITLE: - Combined gemcitabine and CHK1 inhibitor treatment induces apoptosis resistance in cancer stem cell-like cells enriched with tumor spheroids from a non-small cell lung cancer cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Front Med. 2013 Jul 2.

●● Enlace al texto completo (gratis o de pago) [1007/s11684-013-0270-](http://1007/s11684-013-0270-6)

[6](#)

AUTORES / AUTHORS: - Fang DD; Cao J; Jani JP; Tsaparikos K; Blasina A; Kornmann J; Lira ME; Wang J; Jirout Z; Bingham J; Zhu Z; Gu Y; Los G; Hostomsky Z; Vanarsdale T

INSTITUCIÓN / INSTITUTION: - Oncology Research Unit, Pfizer, Inc., 10777 Science Center Drive, San Diego, CA, 92121, USA, douglasfang@yahoo.com.

RESUMEN / SUMMARY: - Evaluating the effects of novel drugs on appropriate tumor models has become crucial for developing more effective therapies that target highly tumorigenic and drug-resistant cancer stem cell (CSC) populations. In this study, we demonstrate that a subset of cancer cells with CSC properties may be enriched into tumor spheroids under stem cell conditions from a non-small cell lung cancer cell line. Treating these CSC-like cells with gemcitabine alone and a combination of gemcitabine and the novel CHK1 inhibitor PF-00477736 revealed that PF-00477736 enhances the anti-proliferative effect of gemcitabine against both the parental and the CSC-like cell populations. However, the CSC-like cells exhibited resistance to gemcitabine-induced apoptosis. Collectively, the spheroid-forming CSC-like cells may serve as a model system for understanding the mechanism underlying the drug resistance of CSCs and for guiding the development of better therapies that can inhibit tumor growth and eradicate CSCs.

[896]

TÍTULO / TITLE: - Clinical advances in molecular biomarkers for cancer diagnosis and therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Jul 16;14(7):14771-84. doi: 10.3390/ijms140714771.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140714771](#)

AUTORES / AUTHORS: - Sethi S; Ali S; Philip PA; Sarkar FH

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201, USA. fsarkar@med.wayne.edu.

RESUMEN / SUMMARY: - Cancer diagnosis is currently undergoing a paradigm shift with the incorporation of molecular biomarkers as part of routine diagnostic panel. The molecular alteration ranges from those involving the DNA, RNA, microRNAs (miRNAs) and proteins. The miRNAs are recently discovered small non-coding endogenous single-stranded RNAs that critically regulates the development, invasion and metastasis of cancers. They are altered in cancers and have the potential to serve as diagnostic markers for cancer. Moreover, deregulating their activity offers novel cancer therapeutic approaches. The availability of high throughput techniques for the identification of altered cellular molecules allowed their use in cancer diagnosis. Their application to a variety of body specimens from blood to tissues has been helpful for appreciating their use in the clinical context. The development of innovative antibodies for immunohistochemical detection of proteins also assists in diagnosis and risk stratification. Overall, the novel cancer diagnostic tools have extended their application as prognostic risk factors and can be used as targets for personalized medicine.

[897]

TÍTULO / TITLE: - Hypericin-photodynamic therapy leads to interleukin-6 secretion by HepG2 cells and their apoptosis via recruitment of BH3 interacting-domain death agonist and caspases.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Jun 27;4:e697. doi: 10.1038/cddis.2013.219.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.219](#)

AUTORES / AUTHORS: - Barathan M; Mariappan V; Shankar EM; Abdullah BJ; Goh KL; Vadivelu J

INSTITUCIÓN / INSTITUTION: - Tropical Infectious Disease Research and Education Center (TIDREC), Department of Medical Microbiology, University of Malaya, 50603 Kuala Lumpur, Malaysia.

RESUMEN / SUMMARY: - Photodynamic therapy (PDT) has emerged as a capable therapeutic modality for the treatment of cancer. PDT is a targeted cancer therapy that reportedly leads to tumor cell apoptosis and/or necrosis by facilitating the secretion of certain pro-inflammatory cytokines and expression of

multiple apoptotic mediators in the tumor microenvironment. In addition, PDT also triggers oxidative stress that directs tumor cell killing and activation of inflammatory responses. However, the cellular and molecular mechanisms underlying the role of PDT in facilitating tumor cell apoptosis remain ambiguous. Here, we investigated the ability of PDT in association with hypericin (HY) to induce tumor cell apoptosis by facilitating the induction of reactive oxygen species (ROS) and secretion of Th1/Th2/Th17 cytokines in human hepatocellular liver carcinoma cell line (HepG2) cells. To discover if any apoptotic mediators were implicated in the enhancement of cell death of HY-PDT-treated tumor cells, selected gene profiling in response to HY-PDT treatment was implemented. Experimental results showed that interleukin (IL)-6 was significantly increased in all HY-PDT-treated cells, especially in 1 µg/ml HY-PDT, resulting in cell death. In addition, quantitative real-time PCR analysis revealed that the expression of apoptotic genes, such as BH3-interacting-domain death agonist (BID), cytochrome complex (CYT-C) and caspases (CASP3, 6, 7, 8 and 9) was remarkably higher in HY-PDT-treated HepG2 cells than the untreated HepG2 cells, entailing that tumor destruction of immune-mediated cell death occurs only in PDT-treated tumor cells. Hence, we showed that HY-PDT treatment induces apoptosis in HepG2 cells by facilitating cytotoxic ROS, and potentially recruits IL-6 and apoptosis mediators, providing additional hints for the existence of alternative mechanisms of anti-tumor immunity in hepatocellular carcinoma, which contribute to long-term suppression of tumor growth following PDT.

[898]

TÍTULO / TITLE: - The cooling effect on proinflammatory cytokines interferon-gamma, tumor necrosis factor-alpha, and nitric oxide in patients with multiple sclerosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - ISRN Neurol. 2013 May 16;2013:964572. doi: 10.1155/2013/964572. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1155/2013/964572](#)

AUTORES / AUTHORS: - Poyraz T; Idiman E; Uysal S; Iyilikci L; Ozakbas S; Coskuner Poyraz E; Idiman F

INSTITUCIÓN / INSTITUTION: - Division of Neuroimmunology, Department of Neurology, Faculty of Medicine, Dokuz Eylul University, 35345 Izmir, Turkey.

RESUMEN / SUMMARY: - Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS) in young adults. The proinflammatory cytokines such as interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha), and nitric oxide (NO) which are known to be produced by inflammatory cells play a key role in the pathogenesis of MS. Some metabolic changes may have an effect on axonal transmission, and white blood cells NO and other inflammatory mediators such as cytokines may be affected from cooling process. In this study, we evaluated

the effects of body cooling procedure on proinflammatory cytokines such as TNF-alpha, IFN-gamma, and NO levels. Twenty patients with MS were evaluated. Thirteen of the patients were women, 7 were men (mean age: 33.6 +/- 7.5 yrs.). Body temperature was reduced by an average of 1 degrees C approximately in 1 hour with using the "Medivance Arctic Sun Temperature Management System" device. In our study, the decrease in TNF-alpha, IFN-gamma levels after the cooling procedure has no statistical significance, whereas the decrease in the mean level of NO level after the cooling procedure is 4.63 +/- 7.4 mumol/L which has statistical significance (P = 0.002). These results suggested that the decrease in NO level improves conduction block in demyelinated axonal segments after cooling procedure in multiple sclerosis.

[899]

TÍTULO / TITLE: - Somatic DNA copy number alterations and their potential clinical utility for predicting lethal prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian J Androl. 2013 Jul 1. doi: 10.1038/aja.2013.82.

●● Enlace al texto completo (gratis o de pago) [1038/aja.2013.82](#)

AUTORES / AUTHORS: - Liu W; Wang L; Xu J

INSTITUCIÓN / INSTITUTION: - 1] Center for Cancer Genomics, Winston-Salem, NC 27157, USA [2] Center for Genomics and Personalized Medicine Research, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.

[900]

TÍTULO / TITLE: - The Functional Significance of MicroRNA-29c in Patients with Colorectal Cancer: A Potential Circulating Biomarker for Predicting Early Relapse.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 28;8(6):e66842. doi: 10.1371/journal.pone.0066842. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0066842](#)

AUTORES / AUTHORS: - Yang IP; Tsai HL; Huang CW; Huang MY; Hou MF; Juo SH; Wang JY

INSTITUCIÓN / INSTITUTION: - Department of Medical Genetics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan ; Department of Nursing, Shu-Zen Junior College of Medicine and Management, Kaohsiung, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND: The recurrence of colorectal cancer (CRC) is frequent within the first year of curative resection surgery and may be unavoidable. microRNAs have been suggested to play roles in carcinogenesis and cancer recurrence. We recently identified microRNA-29c (miRNA-29c) as a predictor of early recurrence in CRC. In the present study, we further

investigated the functions and serum level of miRNA-29c in relation to early recurrence of CRC. METHODS: First we further confirmed overexpression of miRNA-29c in non-early relapse subjects. Gain-of-function in vitro studies were used to evaluate the effect of miRNA-29c on cell proliferation, migration, invasion, and cell cycle progression. The colon cancer cell line Caco2 and a stable clone overexpressing miRNA-29c were xenografted to evaluate the in vivo effect of miRNA-29c in null mice. Finally, circulating miRNA-29c was investigated as a potential biomarker for identifying early relapse. RESULTS: miRNA-29c expression significantly decreased during early relapse compared to non-early relapse in UICC stage II and III CRC patients ($P = 0.021$). In vitro studies showed that overexpression of miRNA-29c inhibited cell proliferation and migration. The cell cycle studies also revealed that miRNA-29c caused an accumulation of the G1 and G2 population. In vivo, miRNA-29c suppressed tumor growth in null mice. The serum miRNA-29c increased significantly in early relapsed patients compared to non-early relapsed patients ($P = 0.012$). CONCLUSIONS: miRNA-29c shows anti-tumorigenesis activity, and preoperative circulating miRNA-29c levels can be used to predict postoperative early relapse of CRC.

[901]

TÍTULO / TITLE: - Melatonin attenuates hippocampal neuron apoptosis and oxidative stress during chronic intermittent hypoxia via up-regulating B-cell lymphoma-2 and down-regulating B-cell lymphoma-2-associated X protein.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Saudi Med J. 2013 Jul;34(7):701-8.

AUTORES / AUTHORS: - Tan X; Guo X; Liu H

INSTITUCIÓN / INSTITUTION: - Wuhan Brain Hospital, General Hospital of the Yangtze River Shipping, Wuhan, China.

RESUMEN / SUMMARY: - OBJECTIVE: To investigate the neuroprotective effect of melatonin against chronic intermittent hypoxia (CIH), the major pathophysiologic features of obstructive sleep apnea syndrome. METHODS: This study was conducted between January 2011 and September 2012 in Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China. Thirty 8-week Wistar rats were randomly divided into 3 groups (10 each): a control group, a vehicle-treated CIH group; and a melatonin-treated (10 mg/kg) CIH group. Rats were exposed to either intermittent hypoxia (IH) (oxygen concentration changing periodically from 21.78 \pm 0.65 to 6.57 \pm 0.57%), or air-air cycling at a rate of 30 cycles/hour, 8 hour/day for 4 weeks. RESULTS: The CIH exposure led to a significant decrease in superoxide dismutase (SOD) activity and anti-apoptotic protein B-cell lymphoma-2 (BCL-2) expression in the hippocampus of CIH group rats compared with that of the control group and melatonin-treated CIH group. In contrast, hippocampal neuronal apoptosis increased significantly in parallel to an augment in 3,4-methylenedioxymphetamine (MDA) content and pro-apoptotic protein Bcl-2-

associated X protein (BAX) expression in CIH group than the other 2 groups. Melatonin administration abrogated the increase in MDA activity, as well as BAX expression, and restored SOD activity and BCL-2 expression to nearly their normal levels. CONCLUSION: These results indicate melatonin can inhibit hippocampal neuron apoptosis following CIH by scavenging reactive oxygen species, up-regulating anti-apoptotic protein BCL-2 and down-regulating pro-apoptotic protein BAX, and thus, alleviate CIH-induced oxidative stress injury and produce neuroprotection effects.

[902]

TÍTULO / TITLE: - The Role of Tumor Necrosis Factor-alpha and Interferon-gamma in Regulating Angiotensin-Like Protein 1 Expression in Lung Microvascular Endothelial Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Allergol Int. 2013 Jun 25.

●● Enlace al texto completo (gratis o de pago) [2332/allergolint.12-OA-0528](#)

AUTORES / AUTHORS: - Nakajima Y; Nakamura Y; Shigeeda W; Tomoyasu M; Deguchi H; Tanita T; Yamauchi K

INSTITUCIÓN / INSTITUTION: - Division of Pulmonary Medicine, Allergy, and Rheumatology, Department of Internal Medicine, Iwate Medical University School of Medicine, Iwate, Japan.

RESUMEN / SUMMARY: - Background: Angiogenesis in the alveolar septa is thought to be a critical factor in pulmonary emphysema. Angiotensin-like protein 1 (AmotL1) is involved in angiogenesis via regulating endothelial cell function. However, the role of AmotL1 in the pathogenesis of pulmonary emphysema has not been elucidated. The objective of this study is to evaluate the expression of AmotL1 in lung tissues from a murine model with emphysema, as well as from patients with chronic obstructive pulmonary disease (COPD). Furthermore, we analyzed the regulation of AmotL1 expression by TNF-alpha and IFN-gamma in endothelial cells in vitro. Methods: Nrf2 knockout mice were exposed to cigarette smoke (CS) for 4 weeks, and the down-regulated genes affecting vascularity in the whole lung were identified by microarray analysis. This analysis revealed that the mRNA expression of AmotL1 decreased in response to CS when compared with air exposure. To confirm the protein levels that were indicated in the microarray data, we determined the expression of AmotL1 in lung tissues obtained from patients with COPD and also determined the expression of AmotL1, NFkappaB and IkappaBalpha in cultured normal human lung microvascular endothelial cells (HLMVECs) that were stimulated by TNF-alpha and IFN-gamma. Results: We found that the number of AmotL1-positive vessels decreased in the emphysema lungs compared with the normal and bronchial asthmatic lungs. IFN-gamma pretreatment diminished the TNF-alpha-induced AmotL1 in the cultured HLMVECs by blocking the degradation of

IkappaB α . Conclusions: These results suggested that IFN-gamma exhibits anti-angiogenesis effects by regulating the expression of TNF- α -induced AmotL1 via NFkappaB in emphysema lungs.

[903]

TÍTULO / TITLE: - SIRT1-Mediated FoxO1 Deacetylation Is Essential for Multidrug Resistance-Associated Protein 2 Expression in Tamoxifen-Resistant Breast Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Pharm. 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1021/mp400287p](#)

AUTORES / AUTHORS: - Choi HK; Cho KB; Phuong NT; Han CY; Han HK; Hien TT; Choi HS; Kang KW

INSTITUCIÓN / INSTITUTION: - BK21 Project Team, College of Pharmacy, Chosun University, Gwangju 501-759, South Korea.

RESUMEN / SUMMARY: - Our previous studies have shown that multidrug resistance protein 2 (MRP2) is overexpressed in tamoxifen-resistant MCF-7 breast cancer cells (TAMR-MCF-7 cells) and forkhead box-containing protein, O subfamily1 (FoxO1), functions as a key regulator of multidrug resistance 1 (MDR1) gene transcription. This study aimed to investigate the role of FoxO1 in regulating MRP2 gene expression in TAMR-MCF-7 cells. The proximal promoter region of the human MRP2 gene contains four putative FoxO binding sites, and MRP2 gene transcription was stimulated by FoxO1 overexpression in MCF-7 cells. Subcellular fractionation and immunoblot analyses revealed that basal MRP2 expression and nuclear levels of FoxO1 were enhanced in TAMR-MCF-7 cells compared to MCF-7 cells and the enhanced MRP2 gene transcription was suppressed by FoxO1 siRNA. Because nuclear localization of FoxO1 is regulated by SIRT1 deacetylase, we were further interested in whether SIRT1 is involved in MRP2 expression. Overexpression of SIRT1 with FoxO1 potentiated the gene transcriptional activity of MRP2, and the basal activity and expression of SIRT1 was increased in TAMR-MCF-7 cells. In addition, SIRT1 inhibition reduced both the nuclear FoxO1 levels and MRP2 expression and enhanced cytotoxic effects of paclitaxel and doxorubicin in TAMR-MCF-7 cells. These results suggest that FoxO1 activation via SIRT1-mediated deacetylation is closely related with up-regulation of MRP2 in TAMR-MCF-7 cells.

[904]

TÍTULO / TITLE: - Antiproliferative Activity of Lavatera cashmeriana- Protease Inhibitors towards Human Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(6):3975-8.

AUTORES / AUTHORS: - Rakashanda S; Qazi AK; Majeed R; Rafiq S; Dar IM; Masood A; Hamid A; Amin S

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, University of Kashmir, Srinagar, J and K, India E-mail : shajrul@rediffmail.com.

RESUMEN / SUMMARY: - Background: Proteases play a regulatory role in a variety of pathologies including cancer, pancreatitis, thromboembolic disorders, viral infections and many others. One of the possible strategies to combat these pathologies seems to be the use of protease inhibitors. LC-pi I, II, III and IV (Lavatera cashmerian-protease inhibitors) have been found in vitro to strongly inhibit trypsin, chymotrypsin and elastase, proteases contributing to tumour invasion and metastasis, indicated possible anticancer effects. The purpose of this study was to check in vitro anticancer activity of these four inhibitors on human lung cancer cell lines. Material and Methods: In order to assess whether these inhibitors induced in vitro cytotoxicity, SRB assay was conducted with THP-1 (leukemia), NCIH322 (lung) and Colo205, HCT-116 (colon) lines. Results: LC-pi I significantly inhibited the cell proliferation of all cells tested and also LC-pi II was active in all except HCT-116. Inhibition of cell growth by LC-pi III and IV was negligible. IC50 values of LC-pi I and II for NCIH322, were less compared to other cell lines suggesting that lung cancer cells are more inhibited. Conclusion: These investigations might point to future preventive as well as curative solutions using plant protease inhibitors for various cancers, especially in the lung, hence warranting their further investigation.

[905]

TÍTULO / TITLE: - Brahmarelated gene 1-associated expression of 9-27 and IFI-27 is involved in acquired cisplatin resistance of gastric cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Sep;8(3):747-50. doi: 10.3892/mmr.2013.1576. Epub 2013 Jul 8.

●● Enlace al texto completo (gratis o de pago) 3892/mmr.2013.1576

AUTORES / AUTHORS: - Lee HR; No HK; Ryu CJ; Park HJ

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Gyeonggi-do 411-706, Republic of Korea.

RESUMEN / SUMMARY: - In order to investigate the mechanism of cisplatin resistance, a cisplatin-resistant human gastric cancer cell line was established. Subsequent to the exposure of the YCC-3 gastric cancer cell line to equal concentrations of cisplatin (II) (cisplatin, CDDP) for 6 months, a cisplatin-resistant cell line was established (YCC3/R). To determine the molecular mechanism of cisplatin resistance in YCC3/R cells, differentially expressed genes (DEGs) were investigated between YCC3 and YCC-3/R by annealing control primer-based reverse transcriptase-polymerase chain reaction (ACP RTPCR) technology. Eleven DEGs were successfully identified and sequenced. Among them, interferon-induced transmembrane protein 1 (927) and interferon alpha-inducible protein 27 (IFI27) were markedly increased in YCC3/R cells. In addition, western blot analysis demonstrated that the Brahmarelated

gene 1 (BRG1), which was observed to selectively activate 927 and IFI27 genes, was overexpressed in YCC3/R cells. The results suggested that the BRG1-associated expression of 927 and IFI27 is involved in cisplatin resistance in gastric cancer cells.

[906]

TÍTULO / TITLE: - Small proline-rich repeat protein 3 enhances the sensitivity of esophageal cancer cells in response to DNA damage-induced apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Oncol. 2013 Jun 13. pii: S1574-7891(13)00084-7. doi: 10.1016/j.molonc.2013.05.005.

●● Enlace al texto completo (gratis o de pago)

1016/j.molonc.2013.05.005

AUTORES / AUTHORS: - Luo A; Chen H; Ding F; Zhang Y; Wang M; Xiao Z; Liu Z

INSTITUCIÓN / INSTITUTION: - State Key Lab of Molecular Oncology, Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing 100021, PR China.

RESUMEN / SUMMARY: - Small proline-rich repeat protein 3 (SPRR3) has been linked with the altered chemoradiosensitivity, however the underlying molecular mechanisms remain elusive. Here, we report that ectopic overexpression of SPRR3 enhanced the sensitivity of cells in response to DNA damage-induced apoptosis via loss of mitochondrial membrane potential (MMP), and increasing activation of caspase 3 in human esophageal cancer cell lines. Conversely, siRNA knockdown of SPRR3 reduced apoptosis. We found that SPRR3 was localized in mitochondria and interacted with Bcl-2 in vivo, thus facilitating Bax mitochondrial translocation and the subsequent release of cytochrome c, and thereby enhancing cell sensitivity to DNA damage stimuli. In clinical samples, expression of SPRR3 was associated with the pathologic response (P = 0.007 in radiotherapy group, P = 0.035 in preoperative radiotherapy group) and good survival of patients with locally advanced esophageal squamous cell carcinoma (ESCC, P = 0.008). Taken together, our results implicate that SPRR3 might serve as a radiation-sensitive predictor of ESCC.

[907]

TÍTULO / TITLE: - A 32-gene risk index: a new prognostic approach for prostate cancer progression.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian J Androl. 2013 Jun 10. doi: 10.1038/aja.2013.85.

●● Enlace al texto completo (gratis o de pago) 1038/aja.2013.85

AUTORES / AUTHORS: - Cai C; Zhong WD; McDougal WS; Wu CL

INSTITUCIÓN / INSTITUTION: - 1] Department of Urology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA [2] Graduate School of Southern Medical University, Guangzhou, Guangdong 510515, China.

[908]

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 Jul 23.

●● Enlace al texto completo (gratis o de pago) [1055/s-0033-1350619](#)

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.

RESUMEN / SUMMARY: - The goal of this study was to investigate the effect and molecular mechanism of cudraflavone B, a prenylated flavonoid isolated from the root bark of *Cudrania tricuspidata*, against oral squamous cell carcinoma cells. We observed that cudraflavone B inhibited proliferation of these cells in a time- and dose-dependent manner. At 15 microM, cudraflavone B induced cell death via apoptosis (characterized by the appearance of nuclear morphology) and increased the accumulation of the sub-G1 peak (portion of apoptotic annexin V positive cells). Treatment with cudraflavone B triggered the mitochondrial apoptotic pathway (indicated by induction of the proapoptotic protein p53 and the p21 and p27 effector proteins), downregulation of cell cycle regulatory proteins (e.g., p-Rb, changing Bax/Bcl-2 ratios, cytochrome-c release), and caspase-3 activation. Cudraflavone B time-dependently activated NF-kappaB, the MAP kinases p38, and ERK, and induced the expression of SIRT1. SIRT1 activator, resveratrol, dose-dependently attenuated the growth-inhibitory and apoptosis-inducing effect of cudraflavone B and blocked cudraflavone B-induced regulatory protein expressions in the mitochondrial pathway such as p53, p21, p27, Bax, caspase-3, and cytochrome-c. Conversely, treatment with SIRT1 inhibitor sirtinol caused opposite effects. These results demonstrate for the first time that the molecular mechanism underlying the antitumor effect in oral squamous cell carcinoma cells is related to the activation of MAPK/and NF-kappaB as well as of the SIRT1 pathway. Therefore, cudraflavone B may be a lead for the development of a potential candidate for human oral squamous cell carcinoma cells.

[909]

TÍTULO / TITLE: - Toxicity of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil for advanced head and neck cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Isr Med Assoc J. 2013 May;15(5):231-5.

AUTORES / AUTHORS: - Billan S; Kaidar-Person O; Atrash F; Doweck I; Haim N; Kuten A; Ronen O

INSTITUCIÓN / INSTITUTION: - Division of Oncology, Rambam Health Care Campus, Haifa, Israel. s_billan@rambam.health.gov.il

RESUMEN / SUMMARY: - BACKGROUND: The role of induction chemotherapy in advanced squamous cell carcinoma of the head and neck (SCCHN) is under constant debate. Surgery, radiotherapy, chemotherapy, and targeted therapies are part of the treatment strategy in these patients, but their sequence remains to be defined. OBJECTIVES: To evaluate the feasibility of induction chemotherapy with docetaxel-cisplatin-5-fluorouracil (TPF) followed by external beam radiotherapy (EBRT) with concomitant chemotherapy or cetuximab (ERT) in the treatment of patients with advanced SCCHN. METHODS: We reviewed the data of all patients with advanced SCCHN, stage III and IV, treated in 2007-2010. Tolerability was assessed and scored according to the proportion of patients completing the planned study protocol. Toxicity was scored using the U.S. National Cancer Institute Common Toxicity Criteria (version 4) for classification of adverse events. RESULTS: The study included 53 patients. TPF was initiated at a reduced dose in 13 patients (25%). Twenty-two patients (41.5%) received primary prophylaxis with granulocyte colony-stimulating factor (GCSF) and 42 (77%) completed treatment according to schedule. During the induction phase one patient (2%) died and 24 (45%) had one or more grade 3-4 complications. The number of patients who developed neutropenia was lower in the group that received primary GCSF prophylaxis. Secondary dose reductions were required in 21% of the patients. CONCLUSIONS: Induction TPF was associated with grade 3-4 toxicity. Prophylaxis with GCSF should be part of the treatment regimen.

[910]

TÍTULO / TITLE: - ANGPT2 promoter methylation is strongly associated with gene expression and prognosis in chronic lymphocytic leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Epigenetics. 2013 May 14;8(7).

AUTORES / AUTHORS: - Martinelli S; Kanduri M; Maffei R; Fiorcari S; Bulgarelli J; Marasca R; Rosenquist R

INSTITUCIÓN / INSTITUTION: - Hematology Unit; Department of Medical and Surgical Sciences; University of Modena and Reggio Emilia; Modena, Italy.

RESUMEN / SUMMARY: - Increasing evidence suggests a key role for angiopoietin-2 (ANGPT2) in influencing the aggressiveness of chronic lymphocytic leukemia (CLL). In the presence of vascular endothelial growth factor (VEGF), ANGPT2 causes vessel destabilization leading to neoangiogenesis. Accordingly, high expression levels of ANGPT2 and high degree of angiogenesis have consistently been associated with poor prognosis in CLL; however, the molecular mechanisms behind the variability in ANGPT2

expression are still to be discovered. Here, for the first time, we investigated the DNA methylation status of the ANGPT2 promoter in a large CLL cohort (n = 88) using pyrosequencing and correlated methylation data with ANGPT2 expression levels, prognostic factors and outcome. Importantly, methylation levels of the ANGPT2 gene correlated inversely with its mRNA expression levels (p < 0.001). Moreover, low ANGPT2 methylation status was highly associated with adverse prognostic markers, shorter time to first treatment and overall survival. Finally, treatment with methyl inhibitors induced re-expression of ANGPT2 in two B-cell lymphoma cell lines, underscoring the importance of DNA methylation in regulating transcriptional silencing of this gene. In conclusion, we believe that the known variability in ANGPT2 expression among CLL patients could be explained by differential promoter DNA methylation and that low methylation levels of the ANGPT2 promoter have an adverse prognostic impact in CLL.

[911]

TÍTULO / TITLE: - miR-17 in imatinib resistance and response to tyrosine kinase inhibitors in chronic myeloid leukemia cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J BUON. 2013 Apr-Jun;18(2):437-41.

AUTORES / AUTHORS: - Firatligil B; Biray Avci C; Baran Y

INSTITUCIÓN / INSTITUTION: - Izmir Institute of Technology, Department of Molecular Biology and Genetics, Izmir, Turkey.

RESUMEN / SUMMARY: - Purpose: In this study we examined the expression levels of miR-17 which possesses oncogenic activities through downregulation of CDKN1A, p21 and E2F1 tumor suppressor genes, in imatinib sensitive and resistant chronic myeloid leukemia (CML) cells. On the other hand, we also determined the expression levels of miR-17 in response to tyrosine kinase inhibitors imatinib, nilotinib and dasatinib used for the treatment of CML. Methods: The expression profiles of miR-17 were analysed by Stem-Loop reverse transcription (RT) polymerase chain reaction (PCR). Results: The results revealed significant increase in the expression levels of miR-17 in imatinib sensitive and resistant cells compared to peripheral blood mononuclear cells (PBMCs). On the other hand, significant decrease was observed in miR-17 levels in response to imatinib, nilotinib and dasatinib. Conclusion: These results may imply that miR-17 can be used for diagnosis and treatment of CML.

[912]

TÍTULO / TITLE: - Apoptosis Induced by Tanshinone IIA and Cryptotanshinone Is Mediated by Distinct JAK/STAT3/5 and SHP1/2 Signaling in Chronic Myeloid Leukemia K562 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med.

2013;2013:805639. doi: 10.1155/2013/805639. Epub 2013 Jun 26.

- Enlace al texto completo (gratis o de pago) [1155/2013/805639](https://doi.org/10.1155/2013/805639)

AUTORES / AUTHORS: - Jung JH; Kwon TR; Jeong SJ; Kim EO; Sohn EJ; Yun M; Kim SH

INSTITUCIÓN / INSTITUTION: - College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.

RESUMEN / SUMMARY: - Though tanshinone IIA and cryptotanshinone possess a variety of biological effects such as anti-inflammatory, antioxidative, antimetabolic, and anticancer effects, the precise molecular targets or pathways responsible for anticancer activities of tanshinone IIA and cryptotanshinone in chronic myeloid leukemia (CML) still remain unclear. In the present study, we investigated the effect of tanshinone IIA and cryptotanshinone on the Janus activated kinase (JAK)/signal transducer and activator of transcription (STAT) signaling during apoptotic process. We found that both tanshinone IIA and cryptotanshinone induced apoptosis by activation of caspase-9/3 and Sub-G1 accumulation in K562 cells. However, they have the distinct JAK/STAT pathway, in which tanshinone IIA inhibits JAK2/STAT5 signaling, whereas cryptotanshinone targets the JAK2/STAT3. In addition, tanshinone IIA enhanced the expression of both SHP-1 and -2, while cryptotanshinone regulated the expression of only SHP-1. Both tanshinone IIA and cryptotanshinone attenuated the expression of bcl-xL, survivin, and cyclin D1. Furthermore, tanshinone IIA augmented synergy with imatinib, a CML chemotherapeutic drug, better than cryptotanshinone in K562 cells. Overall, our findings suggest that the anticancer activity of tanshinone IIA and cryptotanshinone is mediated by the distinct the JAK/STAT3/5 and SHP1/2 signaling, and tanshinone IIA has the potential for combination therapy with imatinib in K562 CML cells.

[913]

TÍTULO / TITLE: - Prognostic value of somatostatin receptor-2 positivity in gastroenteropancreatic neuroendocrine tumors in reference to known prognostic factors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Turk J Gastroenterol. 2012 Dec;23(6):736-40.

AUTORES / AUTHORS: - Yeniay L; Gurcu BI; Unalp O; Yilmaz F; Nart D; Sozbilen M; Coker A

INSTITUCIÓN / INSTITUTION: - Ege University School of Medicine, Department of General Surgery, Izmir, Turkey E-Mail: lyeniay@yahoo.com.

RESUMEN / SUMMARY: - Background/aims: Identification of the predictive factors for the prognosis of gastroenteropancreatic neuroendocrine tumors is important but rather challenging due to the rarity of the condition. This study aimed to examine the association between somatostatin receptor-2 positivity and known prognostic factors for gastroenteropancreatic neuroendocrine tumor to identify the value of somatostatin receptor-2 positivity itself as a predictive factor for prognosis. Materials and Methods: Records of 41 gastroenteropancreatic

neuroendocrine tumor patients (24 females, 17 males) were retrospectively reviewed. The relations between somatostatin receptor-2 positivity and known prognostic factors including tumor stage, Ki-67 positivity, vascular or perineural invasion, lymph node metastasis, presence of necrosis, and soft tissue extension were analyzed. Results: Sixty percent of the patients had histologically confirmed somatostatin receptor-2 positivity with 45% exhibiting focal and 15% showing diffuse staining characteristic. No significant relation was found between somatostatin receptor-2 positivity and any of the known prognostic factors for gastroenteropancreatic neuroendocrine tumor: versus stage, $p=0.67$; vs. lymph node metastasis, $p=0.51$; vs. vascular invasion, $p=0.11$; vs. extension to surrounding soft tissue, $p=0.54$; vs. necrosis, $p=0.23$; vs. lymphatic invasion, $p=0.25$; and vs. perineural invasion, $p=0.42$. Conclusions: Somatostatin receptor-2 positivity, either focal or diffuse, does not seem to predict prognosis in gastroenteropancreatic neuroendocrine tumors. However, growing evidence supports the benefits of somatostatin analogues as adjunctive treatment in this group of patients.

[914]

TÍTULO / TITLE: - Luteolin sensitises drug-resistant human breast cancer cells to tamoxifen via the inhibition of cyclin E2 expression.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Food Chem. 2013 Nov 15;141(2):1553-61. doi: 10.1016/j.foodchem.2013.04.077. Epub 2013 May 2.

●● Enlace al texto completo (gratis o de pago)

[1016/j.foodchem.2013.04.077](#)

AUTORES / AUTHORS: - Tu SH; Ho CT; Liu MF; Huang CS; Chang HW; Chang CH; Wu CH; Ho YS

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Medical Sciences, Taipei Medical University, Taipei, Taiwan; Department of Surgery, Cathay General Hospital, Taipei, Taiwan.

RESUMEN / SUMMARY: - Luteolin is a flavonoid that has been identified in many plant tissues and exhibits chemopreventive or chemosensitising properties against human breast cancer. However, the oncogenic molecules in human breast cancer cells that are inhibited by luteolin treatment have not been identified. This study found that the level of cyclin E2 (CCNE2) mRNA was higher in tumour cells (4.89-fold, ($*$) $P=0.005$) than in normal paired tissue samples as assessed using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) analysis ($n=257$). Further, relatively high levels of CCNE2 protein expression were detected in tamoxifen-resistant (TAM-R) MCF-7 cells. These results showed that the level of CCNE2 protein expression was specifically inhibited in luteolin-treated (5 μ M) TAM-R cells, either in the presence or absence of 4-OH-TAM (100nM). Combined treatment with 4-OH-TAM and luteolin synergistically sensitised the TAM-R cells to 4-OH-TAM. The

results of this study suggest that luteolin can be used as a chemosensitizer to target the expression level of CCNE2 and that it could be a novel strategy to overcome TAM resistance in breast cancer patients.

[915]

TÍTULO / TITLE: - Towards the goal of personalized medicine in gastric cancer—time to move beyond HER2 inhibition. Part I: Targeting receptor tyrosine kinase gene amplification.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Discov Med. 2013 Jun;15(85):333-41.

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 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 focus on the receptor tyrosine kinase (RTK) gene amplification (HER2, FGFR2, MET, EGFR). Part II will devoted to 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.

[916]

TÍTULO / TITLE: - miR-375 targets the p53 gene to regulate cellular response to ionizing radiation and etoposide in gastric cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - DNA Repair (Amst). 2013 Sep;12(9):741-50. doi: 10.1016/j.dnarep.2013.06.002. Epub 2013 Jul 5.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1016/j.dnarep.2013.06.002](#)

AUTORES / AUTHORS: - Liu Y; Xing R; Zhang X; Dong W; Zhang J; Yan Z; Li W; Cui J; Lu Y

INSTITUCIÓN / INSTITUTION: - Laboratory of Molecular Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China.

RESUMEN / SUMMARY: - MicroRNAs (miRNAs) offer a new approach for molecular classification and individual therapy of human cancer due to their regulation of oncogenic pathways. In a previous report, elevated miR-375 was found in recurring gastric cancer, and it was predicted that miR-375 may be a regulator of p53 gene. However, its biological role and mechanism of actions remain unknown. In this study, we characterized the expression level of miR-375 in gastric cancer cell lines - BGC823, MGC803, SGC7901, AGS, N87, MKN45 - using RT-PCR. We found that exogenous expression of miR-375 promoted the growth of AGS cells in both liquid and soft agar media. In agreement with the previous report, overexpression of miR-375 in AGS cells reduced the p53 protein expression level. A luciferase assay demonstrated that miR-375 down-regulated p53 expression through an interaction with the 3' UTR region of p53. In addition, the expression of miR-375 desensitizes cells to ionizing radiation and etoposide. Flow cytometry analyses showed that miR-375 abrogated the cell cycle arrest and apoptosis after DNA damage. These results demonstrate that miR-375 targets p53 to regulate the response to ionizing radiation and etoposide treatment.

[917]

TÍTULO / TITLE: - Predicting factors for biochemical recurrence and oncological outcomes following laparoscopic radical prostatectomy in Rajavithi Hospital, Thailand.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Med Assoc Thai. 2013 May;96(5):569-74.

AUTORES / AUTHORS: - Viriyasiripong S; Akarasakul D; Thaidamrong T; Doungkae S

INSTITUCIÓN / INSTITUTION: - Division of Urology, Department of Surgery, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand. ladyhand@gmail.com

RESUMEN / SUMMARY: - OBJECTIVE: To determine the predicting factor of biochemical recurrence and analysis of pathological and oncological outcomes following laparoscopic radical prostatectomy (LRP) at Rajavithi Hospital in Thailand. MATERIAL AND METHOD: One hundred twenty men underwent laparoscopic radical prostatectomy between October 2006 and December 2011. Four men were excluded due to open surgical conversions and fourteen men were excluded due to lacking of follow-up. The remaining 102 men had a mean preoperative prostate specific antigen of 21.4 ng/ml (ranging from 0.4 to 185) and Gleason score of 6.2 (ranging from 6 to 10). Stage was cT1b in one case (1%), cT1c in 66 (64.7%), cT2 in 28 (27.5%), and cT3 in seven (6.9%). Immediate postoperative adjuvant therapy of twenty-six men was excluded from biochemical recurrence analysis. RESULTS: Mean follow-up period was 19.7

months (median 16, ranging from 2 to 54.8). Pathological stage was pT0N0 in two men (2%), pT2N0 in 78 (76.5%), pT3N0 in 11 (10.8%), and pT2-3N1 in 11 (10.8%). Positive surgical margin (SM) rates increased with higher stage (23.1% in pT2, 63.6% in pT3 and 81.8% in pT2-3N1, $p < 0.0001$). Three-year biochemical recurrence-free survival was 87.1% for pT2N0 and 50% for pT3N0/N1 disease ($p = 0.025$), and 84.2% overall. Univariate analysis for age, preoperative PSA, postoperative Gleason score, pathological stage, and margin status showed that only margin status could be used as a predictor for biochemical recurrence. CONCLUSION: Predicting factor for biochemical recurrence after LRP was positive SM status. From the oncological result, LRP in our experience is a safe and efficacious therapy for localized prostate cancer with acceptable and was consistent with results of previous studies.

[918]

TÍTULO / TITLE: - Antitumor effects of Endostar on non-Hodgkin's lymphoma by regulating endothelial progenitor cells through protein kinase B-dependent pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Acta Biochim Biophys Sin (Shanghai). 2013 Jun 28.

●● Enlace al texto completo (gratis o de pago) 1093/abbs/gmt070

AUTORES / AUTHORS: - Yu D; Wu H; Yang B; Yang K; Liu H; Wu G

INSTITUCIÓN / INSTITUTION: - Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

RESUMEN / SUMMARY: - Endothelial progenitor cells (EPCs) play an important role in non-Hodgkin's lymphoma (NHL) development. Endostar is an anti-angiogenic drug designed to stop cancer by nullifying a tumor's ability to obtain oxygen and nutrients. In this study, we examined the anti-angiogenic activities of Endostar on NHL cell lines and murine xenograft model of NHL in vitro and in vivo, respectively, and explored the underlying antiangiogenic mechanism of Endostar. Results showed that Endostar may inhibit the EPC proliferation by reducing the expression of p-protein kinase B, but not p-ERK expression. Our finding could lead to a better understanding of the effects of Endostar on NHL.

[919]

TÍTULO / TITLE: - Interrogating differences in expression of targeted gene sets to predict breast cancer outcome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 2;13(1):326. doi: 10.1186/1471-2407-13-326.

●● Enlace al texto completo (gratis o de pago) 1186/1471-2407-13-326

AUTORES / AUTHORS: - Andres SA; Brock GN; Wittliff JL

INSTITUCIÓN / INSTITUTION: - Hormone Receptor Laboratory, Department of Biochemistry & Molecular Biology, Brown Cancer Center and the Institute for Molecular Diversity & Drug Design, University of Louisville, Louisville, KY 40292, USA. jlwitt01@louisville.edu.

RESUMEN / SUMMARY: - BACKGROUND: Genomics provides opportunities to develop precise tests for diagnostics, therapy selection and monitoring. From analyses of our studies and those of published results, 32 candidate genes were identified, whose expression appears related to clinical outcome of breast cancer. Expression of these genes was validated by qPCR and correlated with clinical follow-up to identify a gene subset for development of a prognostic test. METHODS: RNA was isolated from 225 frozen invasive ductal carcinomas, and qRT-PCR was performed. Univariate hazard ratios and 95% confidence intervals for breast cancer mortality and recurrence were calculated for each of the 32 candidate genes. A multivariable gene expression model for predicting each outcome was determined using the LASSO, with 1000 splits of the data into training and testing sets to determine predictive accuracy based on the C-index. Models with gene expression data were compared to models with standard clinical covariates and models with both gene expression and clinical covariates. RESULTS: Univariate analyses revealed over-expression of RABEP1, PGR, NAT1, PTP4A2, SLC39A6, ESR1, EVL, TBC1D9, FUT8, and SCUBE2 were all associated with reduced time to disease-related mortality (HR between 0.8 and 0.91, adjusted $p < 0.05$), while RABEP1, PGR, SLC39A6, and FUT8 were also associated with reduced recurrence times. Multivariable analyses using the LASSO revealed PGR, ESR1, NAT1, GABRP, TBC1D9, SLC39A6, and LRBA to be the most important predictors for both disease mortality and recurrence. Median C-indexes on test data sets for the gene expression, clinical, and combined models were 0.65, 0.63, and 0.65 for disease mortality and 0.64, 0.63, and 0.66 for disease recurrence, respectively. CONCLUSIONS: Molecular signatures consisting of five genes (PGR, GABRP, TBC1D9, SLC39A6 and LRBA) for disease mortality and of six genes (PGR, ESR1, GABRP, TBC1D9, SLC39A6 and LRBA) for disease recurrence were identified. These signatures were as effective as standard clinical parameters in predicting recurrence/mortality, and when combined, offered some improvement relative to clinical information alone for disease recurrence (median difference in C-values of 0.03, 95% CI of -0.08 to 0.13). Collectively, results suggest that these genes form the basis for a clinical laboratory test to predict clinical outcome of breast cancer.

[920]

TÍTULO / TITLE: - Synergistic Combination of Small Molecule Inhibitor and RNA Interference against Antiapoptotic Bcl-2 Protein in Head and Neck Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Pharm. 2013 Jun 18.

●● Enlace al texto completo (gratis o de pago) [1021/mp4001662](https://doi.org/10.1371/journal.pone.0066302)

AUTORES / AUTHORS: - Lin YL; Yuksel Durmaz Y; Nor JE; Elsayed ME

INSTITUCIÓN / INSTITUTION: - Department of Biomedical Engineering, Cellular Engineering & Nano-Therapeutics Laboratory, College of Engineering, double dagger Department of Cariology, Restorative Sciences, and Endodontics, School of Dentistry, and section sign Macromolecular Science and Engineering Program, University of Michigan , Ann Arbor, Michigan 48109, United States.

RESUMEN / SUMMARY: - B-cell lymphoma 2 (Bcl-2) is an antiapoptotic protein that is overexpressed in head and neck squamous cell carcinomas, which has been implicated in development of radio- and chemoresistance. Small molecule inhibitors such as AT-101 (a BH3-mimetic drug) have been developed to inhibit the antiapoptotic activity of Bcl-2 proteins, which proved effective in restoring radio- and chemo-sensitivity in head and neck cancer cells. However, high doses of AT-101 are associated with gastrointestinal, hepatic, and fertility side effects, which prompted the search for other Bcl-2 inhibitors. Short interfering RNA (siRNA) proved to inhibit antiapoptotic Bcl-2 protein expression and trigger cancer cell death. However, transforming siRNA molecules into a viable therapy remains a challenge due to the lack of efficient and biocompatible carriers. We report the development of degradable star-shaped polymers that proved to condense anti-Bcl-2 siRNA into “smart” pH-sensitive and membrane-destabilizing particles that shuttle their cargo past the endosomal membrane and into the cytoplasm of head and neck cancer cells. Results show that “smart” anti-Bcl-2 particles reduced the mRNA and protein levels of antiapoptotic Bcl-2 protein in UM-SCC-17B cancer cells by 50-60% and 65-75%, respectively. Results also show that combining “smart” anti-Bcl-2 particles with the IC25 of AT-101 (inhibitory concentration responsible for killing 25% of the cells) synergistically inhibits cancer cell proliferation and increases cell apoptosis, which reduce the survival of UM-SCC-17B cancer cells compared to treatment with AT-101 alone. Results indicate the therapeutic benefit of combining siRNA-mediated knockdown of antiapoptotic Bcl-2 protein expression with low doses of AT-101 for inhibiting the growth of head and neck cancer cells.

[921]

TÍTULO / TITLE: - Expression of Epidermal Growth Factor Receptor Detected by Cetuximab Indicates Its Efficacy to Inhibit and Proliferation of Colorectal Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 18;8(6):e66302. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0066302](https://doi.org/10.1371/journal.pone.0066302)

AUTORES / AUTHORS: - Shigeta K; Hayashida T; Hoshino Y; Okabayashi K; Endo T; Ishii Y; Hasegawa H; Kitagawa Y

INSTITUCIÓN / INSTITUTION: - Keio University, School of Medicine, Department of Surgery, Shinjuku-ku, Tokyo, Japan.

RESUMEN / SUMMARY: - Cetuximab is a chimeric mouse-human monoclonal antibody that targets the human epidermal growth factor receptor (EGFR). However, EGFR expression determined by immunohistochemistry does not predict clinical outcomes of colorectal cancer (CRC) patients treated with cetuximab. Therefore, we evaluated the correlation between EGFR levels detected by cetuximab and drug sensitivities of CRC cell lines (Caco-2, WiDR, SW480, and HCT116) and the A431 epidermoid carcinoma cell line. We used flow cytometry (FCM) to detect EGFR-binding of biotinylated cetuximab on the cell surface. Subcloned cell lines showing the highest and lowest EGFR expression levels were chosen for further study. Cytotoxic assays were used to determine differential responses to cetuximab. Xenograft models treated with cetuximab intraperitoneally to assess sensitivity to cetuximab. Strong responses to cetuximab were specifically exhibited by subcloned cells with high EGFR expression levels. Furthermore, cetuximab inhibited the growth of tumors in xenograft models with high or low EGFR expression levels by 35% and 10%-20%, respectively. We conclude that detection of EGFR expression by cetuximab promises to provide a novel, sensitive, and specific method for predicting the sensitivity of CRC to cetuximab.

[922]

TÍTULO / TITLE: - Expression of aldehyde dehydrogenase after neoadjuvant chemotherapy is associated with expression of hypoxia-inducible factors 1 and 2 alpha and predicts prognosis in locally advanced breast cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clinics (Sao Paulo). 2013 May;68(5). pii: S1807-59322013000500592. doi: 10.6061/clinics/2013(05)03.

●● [Enlace al texto completo \(gratis o de pago\) 6061/clinics/2013\(05\)03](#)

AUTORES / AUTHORS: - Tiezzi DG; Clagnan WS; Mandarano LR; de Sousa CB; Marana HR; Tiezzi MG; de Andrade JM

INSTITUCIÓN / INSTITUTION: - Breast Disease Division Department of Gynecology and Obstetrics, Hospital das Clinicas, Ribeirao Preto School of Medicine, Universidade de Sao Paulo, Ribeirao PretoSP, Brazil.

RESUMEN / SUMMARY: - OBJECTIVE: To analyze the expression of hypoxia-inducible factors (hypoxia-inducible factor 1^a and hypoxia-inducible factor 2^a) and aldehyde dehydrogenase proteins in patients with locally advanced breast carcinoma who were subjected to neoadjuvant chemotherapy. METHODS: We included 90 patients with histologically confirmed stage II and III breast carcinoma who were treated with neoadjuvant chemotherapy between 2000 and 2005. Immunohistochemistry for aldehyde dehydrogenase, hypoxia-inducible factor 1^a, and hypoxia-inducible factor 2^a was performed before and after neoadjuvant chemotherapy. We analyzed the influence of clinical and pathological features on clinical and pathological response, disease-free

survival, and overall survival. RESULTS: An objective clinical response to neoadjuvant chemotherapy was observed in 80% of patients, with 12% showing a complete pathological response. Among all clinical and pathological parameters, only the expression of hypoxia-inducible factor 1^a was associated with a pathological response. A positive association was found between expression of aldehyde dehydrogenase and that of hypoxia-inducible factor 1^a before and after chemotherapy. Aldehyde dehydrogenase expression was associated with expression of hypoxia inducible-factor 2^a in tumors after neoadjuvant treatment. In a univariate analysis, prognosis was influenced by age, pathological response, metastasis to axillary lymph nodes after neoadjuvant chemotherapy, overexpression of hypoxia-inducible factor 2, and the presence of aldehyde dehydrogenase-positive cells within the primary tumor after neoadjuvant chemotherapy. In a multivariate analysis, only age and the presence of aldehyde dehydrogenase-positive cells after chemotherapy were associated with reduced overall survival. CONCLUSION: The presence of aldehyde dehydrogenase-positive cells within the residual tumor after neoadjuvant chemotherapy is associated with an increase in the expression of hypoxia-inducible factor 2^a and with poor prognosis in patients with locally advanced breast cancer.

[923]

TÍTULO / TITLE: - Pseudolaric acid B induces apoptosis in U937 human leukemia cells via caspase-9-mediated activation of the mitochondrial death pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Sep;8(3):787-93. doi: 10.3892/mmr.2013.1571. Epub 2013 Jul 4.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1571](#)

AUTORES / AUTHORS: - Wang JH; Kan L; Shu LH; Wang N; Li NJ; Zhang M

INSTITUCIÓN / INSTITUTION: - Department of Geriatrics, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, P.R. China.

RESUMEN / SUMMARY: - Numerous studies have demonstrated that pseudolaric acid B (PAB) promotes apoptosis in several cancer cell lines. However, thus far, the effect of PAB on human leukemia cells has not been evaluated. In the present study, the antitumor activity and molecular mechanisms of PAB in human leukemia U937 cells were investigated. It was demonstrated that PAB induced U937 cell apoptosis, which was confirmed by typical morphological changes and Annexin Vfluorescein isothiocyanate staining. PAB was observed to activate a caspase-dependent apoptotic pathway in U937 cells through the regulation of the Bcl2 family protein-mediated mitochondrial pathway. Furthermore, the activities of caspase3 and -9 were increased following treatment with PAB. In conclusion, to the best of our knowledge, this study demonstrated for the first time that PAB was able to enhance the apoptosis of U937 cells, at least in part, through the activation of the mitochondrial death

pathway. Moreover, the activation of caspase3 and -9 mediated the apoptotic induction.

[924]

TÍTULO / TITLE: - Organopalladium compound 7b targets mitochondrial thiols and induces caspase-dependent apoptosis in human myeloid leukemia cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Jun 6;4:e658. doi: 10.1038/cddis.2013.190.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.190](#)

AUTORES / AUTHORS: - Moraes VW; Caires AC; Paredes-Gamero EJ; Rodrigues T

INSTITUCIÓN / INSTITUTION: - Centro de Ciências Naturais e Humanas, Universidade Federal do ABC (UFABC), Sao Paulo, Brazil.

RESUMEN / SUMMARY: - The advances in the treatment of chronic myeloid leukemia (CML) during the last years were also accompanied by the development of evading strategies by tumor cells, resulting in chemotherapy resistance in some patients. Patented organopalladium compounds derived from the reaction of N,N-dimethyl-1-phenethylamine (dmpa) with [1,2-ethanebis(diphenylphosphine)] (dppe) exhibited a potent antitumor activity in vivo and in vitro in melanoma cells. We showed here that the cyclopalladated derivative [Pd₂(R(+))C(2), N-dmpa)₂(μ-dppe)Cl₂], named compound 7b, was highly effective to promote cell death in the K562 human leukemia cells and its mechanisms of action were investigated. It was shown that compound 7b was able to promote exclusively apoptotic cell death in K562 cells associated to cytochrome c release and caspase 3 activation. This cytotoxic effect was not observed in normal peripheral mononuclear blood cells. The compound 7b-induced intrinsic apoptotic pathway was triggered by the protein thiol oxidation that resulted in the dissipation of the mitochondrial transmembrane potential. The preventive effect of the dithiothreitol on the compound 7b-induced cell death and all downstream events associated to apoptosis confirmed that death signal was elicited by the thiol oxidation. These findings contribute to the elucidation of the palladacycle 7b-induced cell death mechanism and present this compound as a promising drug in the CML antitumor chemotherapy.

[925]

TÍTULO / TITLE: - Induction of Apoptosis by Fucoidan in Human Leukemia U937 Cells through Activation of p38 MAPK and Modulation of Bcl-2 Family.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mar Drugs. 2013 Jul 4;11(7):2347-64. doi: 10.3390/md11072347.

●● Enlace al texto completo (gratis o de pago) [3390/md11072347](#)

AUTORES / AUTHORS: - Park HS; Hwang HJ; Kim GY; Cha HJ; Kim WJ; Kim ND; Yoo YH; Choi YH

INSTITUCIÓN / INSTITUTION: - Department of Pharmacy, Pusan National University, Busan 609-735, Korea. yhyoo@dau.ac.kr.

RESUMEN / SUMMARY: - The present study investigated possible mechanisms on the apoptosis induction of human leukemic cells by fucoidan, a sulfated polysaccharide found in marine algae. Fucoidan treatment of cells resulted in inhibition of growth and induction of apoptosis, as measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium (MTT) assay, fluorescence microscopy, DNA fragmentation, and flow cytometry analysis. The increase in apoptosis was associated with the proteolytic activation of caspases, Bid cleavage, insertion of pro-apoptotic Bax into the mitochondria, release of cytochrome c from mitochondria to cytosol, and loss of mitochondria membrane potential (MMP) in U937 cells. However, apoptosis induced by fucoidan was attenuated by caspase inhibitors, indicating that fucoidan-induced apoptosis was dependent on the activation of caspases. Furthermore, fucoidan treatment effectively activated the p38 mitogen-activated protein kinase (MAPK) and p38 MAPK inhibitor, SB203580, and significantly reduced fucoidan-induced apoptosis through inhibition of Bax translocation and caspases activation, suggesting that the activation of p38 MAPK may play a key role in fucoidan-induced apoptosis. In addition, the authors found fucoidan-induced significantly attenuated in Bcl-2 overexpressing U937 cells, and pretreatment with fucoidan and HA 14-1, a small-molecule Bcl-2 inhibitor, markedly increased fucoidan-mediated apoptosis in Bcl-2 overexpressing U937 cells. Our findings imply that we may attribute some of the biological functions of p38 MAPK and Bcl-2 to their ability to inhibit fucoidan-induced apoptosis.

[926]

TÍTULO / TITLE: - Down-Regulation of 11beta-Hydroxysteroid Dehydrogenase Type 2 by Bortezomib Sensitizes Jurkat Leukemia T Cells against Glucocorticoid-Induced Apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 24;8(6):e67067. doi: 10.1371/journal.pone.0067067. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0067067](http://dx.doi.org/10.1371/journal.pone.0067067)

AUTORES / AUTHORS: - Tao Y; Gao L; Wu X; Wang H; Yang G; Zhan F; Shi J
INSTITUCIÓN / INSTITUTION: - Department of Hematology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China.

RESUMEN / SUMMARY: - 11beta-hydroxysteroid dehydrogenases type 2 (11beta-HSD2), a key regulator for pre-receptor metabolism of glucocorticoids (GCs) by converting active GC, cortisol, to inactive cortisone, has been shown to be present in a variety of tumors. But its expression and roles have rarely been discussed in hematological malignancies. Proteasome inhibitor bortezomib has been shown to not only possess antitumor effects but also potentiate the

activity of other chemotherapeutics. In this study, we demonstrated that 11beta-HSD2 was highly expressed in two GC-resistant T-cell leukemic cell lines Jurkat and Molt4. In contrast, no 11beta-HSD2 expression was found in two GC-sensitive non-hodgkin lymphoma cell lines Daudi and Raji as well as normal peripheral blood T cells. Inhibition of 11beta-HSD2 by 11beta-HSD inhibitor 18beta-glycyrrhetic acid or 11beta-HSD2 shRNA significantly increased cortisol-induced apoptosis in Jurkat cells. Additionally, pretreatment of Jurkat cells with low-dose bortezomib resulted in increased cellular sensitivity to GC as shown by elevated induction of apoptosis, more cells arrested at G1 stage and up-regulation of GC-induced leucine zipper which is an important mediator of GC action. Furthermore, we clarified that bortezomib could dose-dependently inhibit 11beta-HSD2 messenger RNA and protein levels as well as activity (cortisol-cortisone conversion) through p38 mitogen-activated protein kinase signaling pathway. Therefore, we suggest 11beta-HSD2 is, at least partially if not all, responsible for impaired GC suppression in Jurkat cells and also indicate a novel mechanism by which proteasome inhibitor bortezomib may influence GC action.

[927]

TÍTULO / TITLE: - Upregulation of heat shock protein 27 confers resistance to actinomycin D-induced apoptosis in cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - FEBS J. 2013 Jul 12. doi: 10.1111/febs.12432.

●● Enlace al texto completo (gratis o de pago) [1111/febs.12432](#)

AUTORES / AUTHORS: - Ma W; Teng Y; Hua H; Hou J; Luo T; Jiang Y

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biotherapy, Section of Signal Transduction and Molecular Targeted Therapy, West China Hospital, Sichuan University, Chengdu, China.

RESUMEN / SUMMARY: - Actinomycin D (Act D) is a general transcriptional inhibitor that is approved for the treatment of sarcomas, and Wilms, germ cell and trophoblastic tumors. Little is known about the molecular mechanisms that dictate the sensitivity of cancer cells to Act D. In this study, we investigated the effects of Act D on heat shock proteins (HSPs) and the expression and roles of HSP27 in Act D-induced cancer cell apoptosis. We show that Act D upregulates HSP27 and HSP70 expression in cancer cells, whereas it inhibits HSP90 expression. The upregulation of HSP27 by Act D is not attributable to changes in HSP27 transcription or HSP27 synthesis. HSP27 knockdown leads to an increase in Act D-induced caspase 3 and caspase 7 cleavage, and sensitizes rhabdosarcoma cells and breast cancer cells to Act D-induced apoptosis. We conclude that upregulation of HSP27 represents an adaptive response that compromises the anticancer activity of Act D.

[928]

TÍTULO / TITLE: - Downregulated adaptor protein p66 mitigates autophagy process by low nutrient and enhances apoptotic resistance in human lung adenocarcinoma A549 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - FEBS J. 2013 Jul 1. doi: 10.1111/febs.12416.

●● Enlace al texto completo (gratis o de pago) [1111/febs.12416](#)

AUTORES / AUTHORS: - Zheng Z; Yang J; Zhao D; Gao D; Yan X; Yao Z; Liu Z; Ma Z

INSTITUCIÓN / INSTITUTION: - Tianjin Key Laboratory of Medical Epigenetics, Tianjin Medical University, China.

RESUMEN / SUMMARY: - Macroautophagy or autophagy is a lysosome-dependent process in which enzymatic degradation and recycling of cytosolic components occur in stressful contexts. The mechanisms underlying the signaling from starvation to the regulation of autophagy are not fully understood. We previously showed that the Src family member p66Shc (focal adhesion-associated 66 kDa isoform of the Src homology and collagen) promotes anoikis and suppresses tumor metastasis via k-Ras-dependent control of proliferation and survival. However, the role of p66Shc in low-nutrient-induced autophagy-related pathways remains elusive. In this work, human lung adenocarcinoma A549 cells were used to further investigate the biological effects of p66Shc on autophagy and apoptotic resistance. Here, we show that deficiency of p66Shc mitigates the low-nutrient-induced autophagy process in the levels of microtubule-associated protein 1^a light chain protein 3B (LC3B) conversion, in the number of autophagic vacuoles and in p62/sequestosome 1 protein degradation. However, autophagy-related protein Beclin 1 was not significantly changed during low-nutrient treatment. Furthermore, we found that prolonged phosphorylation of extracellular signaling-regulated kinase (Erk)1/2, but not phosphorylation of Akt is significantly sustained when p66Shc expression is inhibited by shRNA. In addition, cleavage of caspase 7 and poly(ADP-ribose) polymerase, but not caspase 6 and 9 are retarded with this effect compared to the shRNA control cells. Together, these findings suggest the possibility that p66Shc plays a pivotal role in coordinately regulating autophagy process and apoptotic resistance in A549 cells under nutrient-limited conditions.

[929]

TÍTULO / TITLE: - Selective Estrogen Receptor Modulators and Pharmacogenomic Variation in ZNF423 Regulation of BRCA1 Expression: Individualized Breast Cancer Prevention.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Discov. 2013 Jul;3(7):812-825. Epub 2013 Jun 13.

●● Enlace al texto completo (gratis o de pago) [1158/2159-8290.CD-13-0038](#)

AUTORES / AUTHORS: - Ingle JN; Liu M; Wickerham DL; Schaid DJ; Wang L; Mushiroda T; Kubo M; Costantino JP; Vogel VG; Paik S; Goetz MP; Ames MM; Jenkins GD; Batzler A; Carlson EE; Flockhart DA; Wolmark N; Nakamura Y; Weinshilboum RM

INSTITUCIÓN / INSTITUTION: - 1Division of Medical Oncology, 2Division of Clinical Pharmacology, Department of Molecular Pharmacology and Experimental Therapeutics, and 3Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota; 4Section of Cancer Genetics and Prevention and 5Department of Human Oncology, Allegheny General Hospital; 6National Surgical Adjuvant Breast and Bowel Project (NSABP), 7NSABP Biostatistical Center, 8Department of Biostatistics, Graduate School of Public Health, and 9Department of Medical Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania; 10Indiana University, Indianapolis, Indiana; 11RIKEN Center for Genomic Medicine, Tokyo, Japan.

RESUMEN / SUMMARY: - The selective estrogen receptor modulators (SERM) tamoxifen and raloxifene can reduce the occurrence of breast cancer in high-risk women by 50%, but this U.S. Food and Drug Administration-approved prevention therapy is not often used. We attempted to identify genetic factors that contribute to variation in SERM breast cancer prevention, using DNA from the NSABP P-1 and P-2 breast cancer prevention trials. An initial discovery genome-wide association study identified common single-nucleotide polymorphisms (SNP) in or near the ZNF423 and CTSO genes that were associated with breast cancer risk during SERM therapy. We then showed that both ZNF423 and CTSO participated in the estrogen-dependent induction of BRCA1 expression, in both cases with SNP-dependent variation in induction. ZNF423 appeared to be an estrogen-inducible BRCA1 transcription factor. The OR for differences in breast cancer risk during SERM therapy for subjects homozygous for both protective or both risk alleles for ZNF423 and CTSO was 5.71.

[930]

TÍTULO / TITLE: - The aspartate aminotransferase to platelet ratio before chemotherapy predicts adverse events for FOLFOX and XELOX regimens including bevacizumab as the first-line therapy for stage IV, recurrent and metastatic colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Gastrointest Oncol. 2013 Jun;4(2):203-9. doi: 10.3978/j.issn.2078-6891.2013.016.

●● Enlace al texto completo (gratis o de pago) [3978/j.issn.2078-6891.2013.016](#)

AUTORES / AUTHORS: - Sato S; Nakano H; Ishida Y; Otsubo T

INSTITUCIÓN / INSTITUTION: - Department of Surgery, Yokohama Asahi Central and General Hospital, 4-20-1 Wakabadai Asahi-ku Yokohama, 241-0801 Kanagawa, Japan;

RESUMEN / SUMMARY: - BACKGROUND: Oxaliplatin-based chemotherapy for colorectal liver metastasis can induce hepatotoxicity, which increases the risk of liver resection. We previously reported that the aspartate aminotransferase to platelet ratio (APR) before chemotherapy can indicate oxaliplatin-induced splenomegaly and also predict the occurrence of adverse events during chemotherapy. Bevacizumab (BEV) was recently reported to reduce oxaliplatin-induced splenomegaly. Therefore, the aim of the present study was to investigate whether the APR before chemotherapy can predict the splenomegaly and adverse events associated with FOLFOX/BEV or XELOX/BEV in patients with stage IV or recurrent colorectal cancer. METHODS: We performed CT volumetry of the spleen before and 12 weeks after FOLFOX/BEV and XELOX/BEV in 63 patients. The incidence of adverse events, haematological parameters, and biochemistry and urinalysis results were assessed during treatment. RESULTS: An increase in the splenic volume was not observed in the FOLFOX/BEV group, but was significant in the XELOX/BEV group (+5.0% vs. +18.8%, P=0.01). The APR before chemotherapy did not indicate the presence of splenomegaly in the 63 patients, however, it did significantly predict the development of grade 2 or higher adverse events during chemotherapy. CONCLUSIONS: An APR of 0.15 or higher before chemotherapy did not indicate the presence of splenomegaly, but could predict the development of adverse events due to FOLFOX/BEV and XELOX/BEV treatment.

[931]

TÍTULO / TITLE: - Screening for gene mutations: will identification of NT5C2 mutations help predict the chance of relapse in acute lymphoblastic leukemia?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Expert Rev Hematol. 2013 Jun;6(3):223-4. doi: 10.1586/ehm.13.28.

●● Enlace al texto completo (gratis o de pago) [1586/ehm.13.28](#)

AUTORES / AUTHORS: - Meyer JA; Carroll WL; Bhatla T

INSTITUCIÓN / INSTITUTION: - New York University Cancer Institute, New York University Langone Medical Center, New York, NY, USA.

[932]

TÍTULO / TITLE: - Phaseoloideside E, a Novel Natural Triterpenoid Saponin Identified From Entada phaseoloides, Induces Apoptosis in Ec-109 Esophageal Cancer Cells Through Reactive Oxygen Species Generation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Pharmacol Sci. 2013;122(3):163-75. Epub 2013 Jun 20.

AUTORES / AUTHORS: - Mo S; Xiong H; Shu G; Yang X; Wang J; Zheng C; Xiong W; Mei Z

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, South Central University for Nationalities, China.

RESUMEN / SUMMARY: - Phaseoloideside E (PE), a new oleanane-type triterpene saponin, was isolated from the seed kernels of *Entada phaseoloides* (Linn.) Merr. PE had strong cytotoxic activity against an array of malignant cells. Typical morphological and biochemical features of apoptosis were observed in PE-treated Ec-109 cells. PE induced a dose-dependent increase in the sub-G1 fraction of the cell cycle and DNA fragmentation. Decreases in the mitochondrial membrane potential, SOD activity, and GSH content were also observed. Further investigations revealed that PE reduced the ratio of Bcl-2 to Bax and increased the activities of caspase-3 and -9, but this was prevented by Z-VAD-fmk. PE also induced a decrease of the sub-G1 fraction. Furthermore, PE-induced apoptosis was mediated by up-regulating cellular ROS, which was suppressed by cotreating the cells with N-acetylcysteine (NAC). NAC also attenuated the ratio of sub-G1, the generation of DNA fragmentation and the expression of Bcl-2, Bax, caspase-3, and caspase-9. Interestingly, PE did not up-regulate ROS or induce cell death in untransformed cells. These data showed that PE induces cell death through up-regulation of cellular ROS production. Our investigation provides the scientific basis for the traditional application of this herb and suggests the possibility that PE may be used for a treatment of esophageal carcinoma.[Supplementary materials: available only at 1254/jphs.12193FP].

[933]

TÍTULO / TITLE: - Apoptosis Signal-Regulating Kinase 1 Is Involved in Brain-Derived Neurotrophic Factor (BDNF)-Enhanced Cell Motility and Matrix Metalloproteinase 1 Expression in Human Chondrosarcoma Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Jul 25;14(8):15459-78. doi: 10.3390/ijms140815459.

●● Enlace al texto completo (gratis o de pago) 3390/ijms140815459

AUTORES / AUTHORS: - Lin CY; Chang SL; Fong YC; Hsu CJ; Tang CH

INSTITUCIÓN / INSTITUTION: - Graduate Institute of Basic Medical Science, China Medical University, Taichung 404, Taiwan. chtang@mail.cmu.edu.tw.

RESUMEN / SUMMARY: - Chondrosarcoma is the primary malignancy of bone that is characterized by a potent capacity to invade locally and cause distant metastasis, and is therefore associated with poor prognoses. Chondrosarcoma further shows a predilection for metastasis to the lungs. The brain-derived neurotrophic factor (BDNF) is a small molecule in the neurotrophin family of growth factors that is associated with the disease status and outcome of cancers. However, the effect of BDNF on cell motility in human chondrosarcoma cells is mostly unknown. Here, we found that human chondrosarcoma cell lines had significantly higher cell motility and BDNF expression compared to normal chondrocytes. We also found that BDNF increased cell motility and expression of matrix metalloproteinase-1 (MMP-1) in human chondrosarcoma cells. BDNF-mediated cell motility and MMP-1 up-

regulation were attenuated by Trk inhibitor (K252a), ASK1 inhibitor (thioredoxin), JNK inhibitor (SP600125), and p38 inhibitor (SB203580). Furthermore, BDNF also promoted Sp1 activation. Our results indicate that BDNF enhances the migration and invasion activity of chondrosarcoma cells by increasing MMP-1 expression through a signal transduction pathway that involves the TrkB receptor, ASK1, JNK/p38, and Sp1. BDNF thus represents a promising new target for treating chondrosarcoma metastasis.

[934]

TÍTULO / TITLE: - miR203 regulates the proliferation, apoptosis and cell cycle progression of pancreatic cancer cells by targeting Survivin.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Mol Med Rep. 2013 Aug;8(2):379-84. doi: 10.3892/mmr.2013.1504. Epub 2013 May 31.

●● Enlace al texto completo (gratis o de pago) [3892/mmr.2013.1504](#)

AUTORES / AUTHORS: - Xu D; Wang Q; An Y; Xu L

INSTITUCIÓN / INSTITUTION: - Department of General Surgery, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210018, P.R. China.

RESUMEN / SUMMARY: - MicroRNAs have emerged as crucial regulators of tumorigenesis. However, the mechanism by which miR203 is involved in the pathogenesis of pancreatic cancer (PC) remains elusive. In the present study, PC cell lines were used as an experimental model to investigate the expression and functional role of miR203 in PC. miR203 mimic virus, miRNA negative control virus and Survivin shRNA virus were transfected into the PC cell line, CFPAC1. mRNA and protein levels of Survivin were detected using qPCR and western blot analysis. Proliferation, apoptosis and cell cycle profiles were detected by an MTT assay and flow cytometry. Female BALB/cAnu nude mice were used to validate the role of miR203 in vivo. The protein levels of Survivin were found to negatively correlate with miR203 levels in four PC cell lines. A luciferase assay revealed that Survivin was a direct target of miR203. Transfection with miR203 mimic inhibited CFPAC1 cell proliferation and induced apoptosis and G1 phase cell cycle arrest, similar to knockdown of Survivin. In the in vivo nude mouse model, the downregulation of Survivin by knockdown of Survivin or transfection with miR203 mimic inhibited tumor growth. Results of the current study indicate that miR203 regulates the proliferation, apoptosis and cell cycle progression of PC cells by targeting Survivin.

[935]

TÍTULO / TITLE: - Anaplastic lymphoma kinase gene rearrangement and non-small cell lung cancer management: a step forward in personalized therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clinics (Sao Paulo). 2013 May;68(5). pii: S1807-59322013000500726. doi: 10.6061/clinics/2013(05)24.

- Enlace al texto completo (gratis o de pago) [6061/clinics/2013\(05\)24](https://doi.org/10.1371/journal.pone.0065369)

AUTORES / AUTHORS: - De Mello RA; Araujo A

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, Instituto Portugues de Oncologia do Porto Francisco Gentil, Porto, Portugal.

[936]

TÍTULO / TITLE: - MSH3 mismatch repair protein regulates sensitivity to cytotoxic drugs and a histone deacetylase inhibitor in human colon carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 May 28;8(5):e65369. doi: 10.1371/journal.pone.0065369. Print 2013.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0065369](https://doi.org/10.1371/journal.pone.0065369)

AUTORES / AUTHORS: - Park JM; Huang S; Tougeron D; Sinicrope FA

INSTITUCIÓN / INSTITUTION: - Mayo Clinic and Mayo Cancer Center, Rochester, Minnesota, United States of America.

RESUMEN / SUMMARY: - BACKGROUND: MSH3 is a DNA mismatch repair (MMR) gene that undergoes frequent somatic mutation in colorectal cancers (CRCs) with MMR deficiency. MSH3, together with MSH2, forms the MutSbeta heteroduplex that interacts with interstrand cross-links induced by drugs such as cisplatin. To date, the impact of MSH3 on chemosensitivity is unknown. METHODS: We utilized isogenic HCT116 (MLH1-/MSH3-) cells where MLH1 is restored by transfer of chromosome 3 (HCT116+ch3) and also MSH3 by chromosome 5 (HCT116+3+5). We generated HCT116+3+5, SW480 (MLH1+/MSH3+) and SW48 (MLH1-/MSH3+) cells with shRNA knockdown of MSH3. Cells were treated with 5-fluorouracil (5-FU), SN-38, oxaliplatin, or the histone deacetylase (HDAC) inhibitor PCI-24781 and cell viability, clonogenic survival, DNA damage and apoptosis were analyzed. RESULTS: MSH3-deficient vs proficient CRC cells showed increased sensitivity to the irinotecan metabolite SN-38 and to oxaliplatin, but not 5-FU, as shown in assays for apoptosis and clonogenic survival. In contrast, suppression of MLH1 attenuated the cytotoxic effect of 5-FU, but did not alter sensitivity to SN-38 or oxaliplatin. The impact of MSH3 knockdown on chemosensitivity to SN-38 and oxaliplatin was maintained independent of MLH1 status. In MSH3-deficient vs proficient cells, SN-38 and oxaliplatin induced higher levels of phosphorylated histone H2AX and Chk2, and similar results were found in MLH1-proficient SW480 cells. MSH3-deficient vs proficient cells showed increased 53BP1 nuclear foci after irradiation, suggesting that MSH3 can regulate DNA double strand break (DSB) repair. We then utilized PCI-24781 that interferes with homologous recombination (HR) indicated by a reduction in Rad51 expression. The addition of PCI-24781 to oxaliplatin enhanced cytotoxicity to a greater extent compared to either drug alone. CONCLUSION: MSH3 status can regulate the DNA damage response and extent of apoptosis induced by chemotherapy. The ability of MSH3 to regulate chemosensitivity was

independent of MLH1 status. PCI-24781-mediated impairment of HR enhanced oxaliplatin sensitivity, suggesting that reduced DSB repair capacity may be contributory.

[937]

TÍTULO / TITLE: - Promoter DNA methylation pattern identifies prognostic subgroups in childhood T-cell acute lymphoblastic leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 6;8(6):e65373. doi: 10.1371/journal.pone.0065373. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0065373](https://doi.org/10.1371/journal.pone.0065373)

AUTORES / AUTHORS: - Borssen M; Palmqvist L; Karrman K; Abrahamsson J; Behrendtz M; Heldrup J; Forestier E; Roos G; Degerman S

INSTITUCIÓN / INSTITUTION: - Department of Medical Biosciences, Pathology, Umea University, Umea, Sweden.

RESUMEN / SUMMARY: - BACKGROUND: Treatment of pediatric T-cell acute lymphoblastic leukemia (T-ALL) has improved, but there is a considerable fraction of patients experiencing a poor outcome. There is a need for better prognostic markers and aberrant DNA methylation is a candidate in other malignancies, but its potential prognostic significance in T-ALL is hitherto undecided. DESIGN AND METHODS: Genome wide promoter DNA methylation analysis was performed in pediatric T-ALL samples (n = 43) using arrays covering >27000 CpG sites. Clinical outcome was evaluated in relation to methylation status and compared with a contemporary T-ALL group not tested for methylation (n = 32). RESULTS: Based on CpG island methylator phenotype (CIMP), T-ALL samples were subgrouped as CIMP+ (high methylation) and CIMP- (low methylation). CIMP- T-ALL patients had significantly worse overall and event free survival (p = 0.02 and p = 0.001, respectively) compared to CIMP+ cases. CIMP status was an independent factor for survival in multivariate analysis including age, gender and white blood cell count. Analysis of differently methylated genes in the CIMP subgroups showed an overrepresentation of transcription factors, ligands and polycomb target genes. CONCLUSIONS: We identified global promoter methylation profiling as being of relevance for subgrouping and prognostication of pediatric T-ALL.

[938]

TÍTULO / TITLE: - RNA-Seq Differentiates Tumour and Host mRNA Expression Changes Induced by Treatment of Human Tumour Xenografts with the VEGFR Tyrosine Kinase Inhibitor Cediranib.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 19;8(6):e66003. Print 2013.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0066003](https://doi.org/10.1371/journal.pone.0066003)

AUTORES / AUTHORS: - Bradford JR; Farren M; Powell SJ; Runswick S; Weston SL; Brown H; Delpuech O; Wappett M; Smith NR; Carr TH; Dry JR; Gibson NJ; Barry ST

INSTITUCIÓN / INSTITUTION: - Oncology, AstraZeneca Pharmaceuticals, Alderley Park, Cheshire, United Kingdom.

RESUMEN / SUMMARY: - Pre-clinical models of tumour biology often rely on propagating human tumour cells in a mouse. In order to gain insight into the alignment of these models to human disease segments or investigate the effects of different therapeutics, approaches such as PCR or array based expression profiling are often employed despite suffering from biased transcript coverage, and a requirement for specialist experimental protocols to separate tumour and host signals. Here, we describe a computational strategy to profile transcript expression in both the tumour and host compartments of pre-clinical xenograft models from the same RNA sample using RNA-Seq. Key to this strategy is a species-specific mapping approach that removes the need for manipulation of the RNA population, customised sequencing protocols, or prior knowledge of the species component ratio. The method demonstrates comparable performance to species-specific RT-qPCR and a standard microarray platform, and allowed us to quantify gene expression changes in both the tumour and host tissue following treatment with cediranib, a potent vascular endothelial growth factor receptor tyrosine kinase inhibitor, including the reduction of multiple murine transcripts associated with endothelium or vessels, and an increase in genes associated with the inflammatory response in response to cediranib. In the human compartment, we observed a robust induction of hypoxia genes and a reduction in cell cycle associated transcripts. In conclusion, the study establishes that RNA-Seq can be applied to pre-clinical models to gain deeper understanding of model characteristics and compound mechanism of action, and to identify both tumour and host biomarkers.

[939]

TÍTULO / TITLE: - Bonellia albiflora: A Mayan Medicinal Plant That Induces Apoptosis in Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:823453. doi: 10.1155/2013/823453. Epub 2013 Jun 17.

- Enlace al texto completo (gratis o de pago) [1155/2013/823453](https://doi.org/10.1155/2013/823453)

AUTORES / AUTHORS: - Moo-Puc R; Chale-Dzul J; Caamal-Fuentes E

INSTITUCIÓN / INSTITUTION: - Unidad de Investigacion Medica Yucatan, Unidad Medica de Alta Especialidad, Centro Medico Ignacio Garcia Tellez, Instituto Mexicano del Seguro Social, 41 No. 439 x 32 y 34, Colonia Industrial CP, 97150 Merida, YUC, Mexico.

RESUMEN / SUMMARY: - Few studies have been carried out on the medical flora of Mexico's Yucatan Peninsula in search for new therapeutic agents, in particular against cancer. In this paper, we evaluated the cytotoxic potential of the extract of *Bonellia albiflora*, a plant utilized in the traditional Mayan medicine for treatment of chronic injuries of the mouth. We carried out the methanolic extracts of different parts of the plant by means of extraction with the Soxhlet equipment. We conducted liquid-liquid fractions on each extract with solvents of increasing polarity. All extracts and fractions were evaluated for cytotoxic activity versus four human cancer cell lines and one normal cell line through a tetrazolium dye reduction (MTT) assay in 96-well cell culture plates. The methanolic root-bark extract possessed much greater cytotoxic activity in the human oropharyngeal cancer cell line (KB); its hexanic fraction concentrated the active metabolites and induced apoptosis with the activation of caspases 3 and 8. The results demonstrate the cytotoxic potential of the *B. albiflora* hexanic fraction and substantiate the importance of the study of the traditional Mayan medicinal plants.

[940]

TÍTULO / TITLE: - Targeting mTOR to Overcome Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance in Non-Small Cell Lung Cancer Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 16;8(7):e69104. doi: 10.1371/journal.pone.0069104. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1371/journal.pone.0069104](https://doi.org/10.1371/journal.pone.0069104)

AUTORES / AUTHORS: - Fei SJ; Zhang XC; Dong S; Cheng H; Zhang YF; Huang L; Zhou HY; Xie Z; Chen ZH; Wu YL

INSTITUCIÓN / INSTITUTION: - Guangdong Lung Cancer Institute, Medical Research Center of Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China ; Graduate School of Southern Medical University, Guangzhou, China.

RESUMEN / SUMMARY: - AIMS: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown dramatic clinical benefits in advanced non-small cell lung cancer (NSCLC); however, resistance remains a serious problem in clinical practice. The present study analyzed mTOR-associated signaling-pathway differences between the EGFR TKI-sensitive and -resistant NSCLC cell lines and investigated the feasibility of targeting mTOR with specific mTOR inhibitor in EGFR TKI resistant NSCLC cells. METHODS: We selected four different types of EGFR TKI-sensitive and -resistant NSCLC cells: PC9, PC9GR, H1650 and H1975 cells as models to detect mTOR-associated signaling-pathway differences by western blot and Immunoprecipitation and evaluated the antiproliferative effect and cell cycle arrest of ku-0063794 by MTT method and flow cytometry. RESULTS: In the

present study, we observed that mTORC2-associated Akt ser473-FOXO1 signaling pathway in a basal state was highly activated in resistant cells. In vitro mTORC1 and mTORC2 kinase activities assays showed that EGFR TKI-resistant NSCLC cell lines had higher mTORC2 kinase activity, whereas sensitive cells had higher mTORC1 kinase activity in the basal state. The ATP-competitive mTOR inhibitor ku-0063794 showed dramatic antiproliferative effects and G1-cell cycle arrest in both sensitive and resistant cells. Ku-0063794 at the IC50 concentration effectively inhibited both mTOR and p70S6K phosphorylation levels; the latter is an mTORC1 substrate and did not upregulate Akt ser473 phosphorylation which would be induced by rapamycin and resulted in partial inhibition of FOXO1 phosphorylation. We also observed that EGFR TKI-sensitive and -resistant clinical NSCLC tumor specimens had higher total and phosphorylated p70S6K expression levels. CONCLUSION: Our results indicate mTORC2-associated signaling-pathway was hyperactivated in EGFR TKI-resistant cells and targeting mTOR with specific mTOR inhibitors is likely a good strategy for patients with EGFR mutant NSCLC who develop EGFR TKI resistance; the potential specific roles of mTORC2 in EGFR TKI-resistant NSCLC cells were still unknown and should be further investigated.

[941]

TÍTULO / TITLE: - Apoptotic effect of tolfenamic acid on MDA-MB-231 breast cancer cells and xenograft tumors.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Clin Biochem Nutr. 2013 Jul;53(1):21-6. doi: 10.3164/jcbn.12-78. Epub 2013 Jun 29.

●● Enlace al texto completo (gratis o de pago) [3164/jcbn.12-78](#)

AUTORES / AUTHORS: - Kim HJ; Cho SD; Kim J; Kim SJ; Choi C; Kim JS; Nam JS; Han Kwon K; Kang KS; Jung JY

INSTITUCIÓN / INSTITUTION: - Department of Companion and Laboratory Animal Science, Kongju National University, Yesan 340-702, Republic of Korea.

RESUMEN / SUMMARY: - Recent studies have indicated that non-steroidal anti-inflammatory drug (NSAID), particularly tolfenamic acid, can inhibit proliferation and induce apoptosis in various cancer cells. Breast cancer represents one-third of all cancers diagnosed in women and is the second leading cause of cancer death in Western European and North American women. In the present study, we investigated the apoptotic effect of tolfenamic acid in MDA-MB-231 estrogen receptor-negative human breast carcinoma cells and in a xenograft tumor model. Treatment of cells with tolfenamic acid significantly decreased cell viability in a concentration-dependent manner. Notably, tolfenamic acid increased apoptosis-related proteins, such as p53 and p21, within 48 h. Furthermore, in vivo experiments showed that tolfenamic acid treatment resulted in a significant reduction in tumor volume over 5 weeks. Immunohistochemistry results showed that apoptosis-related protein induction by tolfenamic acid was significantly higher in the 50 mg/kg-treated group

compared to the control group. Together, these results indicate that tolfenamic acid induces apoptosis in MDA-MB-231 breast cancer cells and tumor xenograft model and it may be a potential chemotherapeutic agent against breast cancer.

[942]

TÍTULO / TITLE: - Silencing CDK4 radiosensitizes breast cancer cells by promoting apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Div. 2013 Jul 25;8(1):10. doi: 10.1186/1747-1028-8-10.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1747-1028-8-10](#)

AUTORES / AUTHORS: - Hagen KR; Zeng X; Lee MY; Tucker Kahn S; Harrison Pitner MK; Zaky SS; Liu Y; O'Regan RM; Deng X; Saavedra HI

INSTITUCIÓN / INSTITUTION: - Department of Radiation Oncology, Emory University School of Medicine, Atlanta, USA. hsaaved@emory.edu.

RESUMEN / SUMMARY: - **BACKGROUND:** The discovery of molecular markers associated with various breast cancer subtypes has greatly improved the treatment and outcome of breast cancer patients. Unfortunately, breast cancer cells acquire resistance to various therapies. Mounting evidence suggests that resistance is rooted in the deregulation of the G1 phase regulatory machinery. **METHODS:** To address whether deregulation of the G1 phase regulatory machinery contributes to radiotherapy resistance, the MCF10A immortalized human mammary epithelial cell line, ER-PR-Her2+ and ER-PR-Her2- breast cancer cell lines were irradiated. Colony formation assays measured radioresistance, while immunocytochemistry, Western blots, and flow cytometry measured the cell cycle, DNA replication, mitosis, apoptosis, and DNA breaks. **RESULTS:** Molecular markers common to all cell lines were overexpressed, including cyclin A1 and cyclin D1, which impinge on CDK2 and CDK4 activities, respectively. We addressed their potential role in radioresistance by generating cell lines stably expressing small hairpin RNAs (shRNA) against CDK2 and CDK4. None of the cell lines knocked down for CDK2 displayed radiosensitization. In contrast, all cell lines knocked down for CDK4 were significantly radiosensitized, and a CDK4/CDK6 inhibitor sensitized MDA-MB-468 to radiation induced apoptosis. Our data showed that silencing CDK4 significantly increases radiation induced cell apoptosis in cell lines without significantly altering cell cycle progression, or DNA repair after irradiation. Our results indicate lower levels of phospho-Bad at ser136 upon CDK4 silencing and ionizing radiation, which has been shown to signal apoptosis. **CONCLUSION:** Based on our data we conclude that knockdown of CDK4 activity sensitizes breast cancer cells to radiation by activating apoptosis pathways.

[943]

TÍTULO / TITLE: - Glasgow Prognostic Score As a Prognostic Factor in Metastatic Castration-Resistant Prostate Cancer Treated With Docetaxel-Based Chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Clin Genitourin Cancer. 2013 Jun 28. pii: S1558-7673(13)00081-5. doi: 10.1016/j.clgc.2013.04.020.

●● Enlace al texto completo (gratis o de pago) 1016/j.clgc.2013.04.020

AUTORES / AUTHORS: - Linton A; Pond G; Clarke S; Vardy J; Galsky M; Sonpavde G

INSTITUCIÓN / INSTITUTION: - Sydney Cancer Centre, Concord Repatriation General Hospital, Concord, Australia; Sydney Medical School, University of Sydney, Sydney, Australia.

RESUMEN / SUMMARY: - BACKGROUND: The modified Glasgow Prognostic Score (mGPS), derived from C-reactive protein (CRP) and albumin levels, and the neutrophil-lymphocyte ratio (NLR) have demonstrated prognostic significance in a number of malignancies. PATIENTS AND METHODS: Baseline mGPS and NLR were calculated in a prospective cohort of chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) (AT-101-CS-205 trial) who received docetaxel and prednisone +/- AT101. Cox proportional hazards regression models estimated their effects on overall survival (OS). RESULTS: Of 220 eligible patients, mGPS and neutrophil and lymphocyte counts were available for 184, 193, and 112 patients, respectively. Albumin (hazard ratio [HR], 0.28; 95% confidence interval [CI]: 0.14-0.56; P < .001) and CRP (HR, 1.22; 95% CI, 1.00-1.48; P = .048) were independently prognostic for OS. An association between mGPS and OS was found (HR, 1.87; 95% CI, 1.35-2.59; P < .001; median survival, 23.5 months at mGPS 0 vs. 9.8 months at mGPS 2). mGPS was significant after controlling for 3 previously published nomograms or NLR (P <= .001). NLR was not prognostic for OS (HR, 0.98; P = .91), and no association between mGPS and toxicity was noted. CONCLUSION: Our results demonstrate the prognostic role of the mGPS in mCRPC over variables previously identified. mGPS is inexpensive, easily measured, and could be incorporated into routine clinical testing if our results are confirmed in a subsequent validation study. The utility of the NLR in mCRPC remains uncertain despite evidence in other malignancies.

[944]

TÍTULO / TITLE: - The omega-3 polyunsaturated fatty acid DHA induces simultaneous apoptosis and autophagy via mitochondrial ROS-mediated Akt-mTOR signaling in prostate cancer cells expressing mutant p53.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:568671. doi: 10.1155/2013/568671. Epub 2013 Jun 10.

●● Enlace al texto completo (gratis o de pago) 1155/2013/568671

AUTORES / AUTHORS: - Shin S; Jing K; Jeong S; Kim N; Song KS; Heo JY; Park JH; Seo KS; Han J; Park JI; Kweon GR; Park SK; Wu T; Hwang BD; Lim K

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry, College of Medicine, Chungnam National University, Daejeon 301-747, Republic of Korea.

RESUMEN / SUMMARY: - Docosahexaenoic acid (DHA) induces autophagy-associated apoptotic cell death in wild-type p53 cancer cells via regulation of p53. The present study investigated the effects of DHA on PC3 and DU145 prostate cancer cell lines harboring mutant p53. Results show that, in addition to apoptosis, DHA increased the expression levels of lipidated form LC3B and potently stimulated the autophagic flux, suggesting that DHA induces both autophagy and apoptosis in cancer cells expressing mutant p53. DHA led to the generation of mitochondrial reactive oxygen species (ROS), as shown by the mitochondrial ROS-specific probe mitoSOX. Similarly, pretreatment with the antioxidant N-acetyl-cysteine (NAC) markedly inhibited both the autophagy and the apoptosis triggered by DHA, indicating that mitochondrial ROS mediate the cytotoxicity of DHA in mutant p53 cells. Further, DHA reduced the levels of phospho-Akt and phospho-mTOR in a concentration-dependent manner, while NAC almost completely blocked that effect. Collectively, these findings present a novel mechanism of ROS-regulated apoptosis and autophagy that involves Akt-mTOR signaling in prostate cancer cells with mutant p53 exposed to DHA.

[945]

TÍTULO / TITLE: - Inhibitors Of Apoptotic Proteins: New Targets For Anti-Cancer Therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Chem Biol Drug Des. 2013 Jun 21. doi: 10.1111/cbdd.12176.

●● Enlace al texto completo (gratis o de pago) [1111/cbdd.12176](#)

AUTORES / AUTHORS: - Saleem M; Qadir MI; Perveen N; Ahmad B; Saleem U; Irshad T; Ahmad B

INSTITUCIÓN / INSTITUTION: - College of Pharmacy, GC University, Faisalabad, Pakistan; University College of Pharmacy, University of the Punjab, Lahore, Pakistan.

RESUMEN / SUMMARY: - Inhibitors of apoptotic proteins (IAPs) can play an important role in inhibiting apoptosis by exerting their negative action on caspases (apoptotic proteins). There are eight proteins in this family: NAIP/BIRC1/NLRB, cellular IAP1 (cIAP1)/human IAP2/ BIRC2, cellular IAP2 (cIAP2)/human IAP1/BIRC3, X-linked IAP (XIAP)/BIRC4, survivin/BIRC5, baculoviral IAP repeat (BIR)-containing ubiquitin-conjugating enzyme/apollon/BIRC6, livin/melanoma-IAP (ML-IAP)/BIRC7/KIAP and testis-specific IAP (Ts-IAP)/hILP-2/BIRC8. Deregulation of these inhibitors of apoptotic proteins (IAPs) may push cell towards cancer and neurodegenerative disorders. Inhibitors of apoptotic proteins (IAPs) may provide new target for anticancer therapy. Drugs may be developed that are inhibiting these IAPs to

induce apoptosis in cancerous cells. This article is protected by copyright. All rights reserved.

[946]

TÍTULO / TITLE: - Indoleamine 2,3-dioxygenase activity and clinical outcome following induction chemotherapy and concurrent chemoradiation in Stage III non-small cell lung cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncoimmunology. 2013 Mar 1;2(3):e23428.

●● Enlace al texto completo (gratis o de pago) [4161/onci.23428](#)

AUTORES / AUTHORS: - Creelan BC; Antonia S; Bepler G; Garrett TJ; Simon GR; Soliman HH

INSTITUCIÓN / INSTITUTION: - University of South Florida; Tampa FL USA.

RESUMEN / SUMMARY: - Indoleamine 2,3-dioxygenase (IDO) has recently been proposed to account for tumor-induced immunosuppression by influencing the conversion of tryptophan (Trp) into kynurenine (Kyn). The objective of our study was to correlate IDO activity with disease outcome in non-small cell lung cancer (NSCLC) patients treated with multimodal combination therapy. In a single-arm Phase II trial involving induction gemcitabine and carboplatin followed by concurrent paclitaxel, carboplatin and 74 Gy thoracic radiation in stage III NSCLC patients, plasma was drawn at baseline, post-induction, and post-concurrent therapy. The mean plasma Kyn/Trp ratio was used as a surrogate indicator of IDO activity. The 33 participants were distributed as follows: 15 females, 18 males; median age = 62; median overall survival (OS) = 22.4 (95% CI 19.3-25.1) months; median progression-free survival (PFS) = 11.5 (95% CI 6.7-16.3) months. The mean Kyn/Trp ratio at baseline (4.5 +/- 2.8) was higher than that of healthy controls (2.9 +/- 1.9, p = 0.03) and increased after induction therapy (5.2 +/- 3.2, p = 0.08) and chemoradiation (5.8 +/- 3.9, p = 0.01). The post-treatment Kyn/Trp ratio and radiologic responses were not significantly associated at any time point. No significant correlation was found between baseline Kyn/Trp ratios and OS (HR = 1.1, 95% CI 0.45-2.5) or PFS (HR = 0.74, 95% CI 0.30-1.82). A post-induction chemotherapy increase in IDO activity portended worse OS (HR = 0.43, 95% CI 0.19-0.95, p = 0.037) and PFS (HR = 0.47, 95% CI 0.22-1.0, p = 0.055). This observed increase in IDO transcription may be a means for tumors to evade immunosurveillance.

[947]

TÍTULO / TITLE: - Candidate biomarkers for genetic and clinicopathological diagnosis of endometrial cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int J Mol Sci. 2013 Jun 6;14(6):12123-37. doi: 10.3390/ijms140612123.

●● Enlace al texto completo (gratis o de pago) [3390/ijms140612123](#)

AUTORES / AUTHORS: - Banno K; Nogami Y; Kisu I; Yanokura M; Umene K; Masuda K; Kobayashi Y; Yamagami W; Susumu N; Aoki D

INSTITUCIÓN / INSTITUTION: - Department of Obstetrics and Gynecology, School of Medicine, Keio University, Shinanomachi 35 Shinjuku-ku, Tokyo 160-8582, Japan. kbanno@z7.keio.jp.

RESUMEN / SUMMARY: - The recent increase in the frequency of endometrial cancer has emphasized the need for accurate diagnosis and improved treatment. The current diagnosis is still based on conventional pathological indicators, such as clinical stage, tumor differentiation, invasion depth and vascular invasion. However, the genetic mechanisms underlying endometrial cancer have gradually been determined, due to developments in molecular biology, leading to the possibility of new methods of diagnosis and treatment planning. New candidate biomarkers for endometrial cancer include those for molecular epigenetic mutations, such as microRNAs. These biomarkers may permit earlier detection of endometrial cancer and prediction of outcomes and are likely to contribute to future personalized therapy for endometrial cancer.

[948]

TÍTULO / TITLE: - Cucurbitane Triterpenoid from *Momordica charantia* Induces Apoptosis and Autophagy in Breast Cancer Cells, in Part, through Peroxisome Proliferator-Activated Receptor gamma Activation.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:935675. doi: 10.1155/2013/935675. Epub 2013 Jun 13.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/935675](#)

AUTORES / AUTHORS: - Weng JR; Bai LY; Chiu CF; Hu JL; Chiu SJ; Wu CY

INSTITUCIÓN / INSTITUTION: - Department of Biological Science and Technology, China Medical University, Taichung 40402, Taiwan.

RESUMEN / SUMMARY: - Although the antitumor activity of the crude extract of wild bitter melon (*Momordica charantia* L.) has been reported, its bioactive constituents and the underlying mechanism remain undefined. Here, we report that 3 beta, 7 beta -dihydroxy-25-methoxycucurbita-5,23-diene-19-al (DMC), a cucurbitane-type triterpene isolated from wild bitter melon, induced apoptotic death in breast cancer cells through peroxisome proliferator-activated receptor (PPAR) gamma activation. Luciferase reporter assays indicated the ability of DMC to activate PPAR gamma, and pharmacological inhibition of PPAR gamma protected cells from DMC's antiproliferative effect. Western blot analysis indicated that DMC suppressed the expression of many PPAR gamma-targeted signaling effectors, including cyclin D1, CDK6, Bcl-2, XIAP, cyclooxygenase-2, NF-kappa B, and estrogen receptor alpha, and induced endoplasmic reticulum stress, as manifested by the induction of GADD153 and GRP78 expression. Moreover, DMC inhibited mTOR-p70S6K signaling through Akt downregulation and AMPK activation. The ability of DMC to activate AMPK in liver kinase (LK) B1-deficient MDA-MB-231 cells suggests that this activation

was independent of LKB1-regulated cellular metabolic status. However, DMC induced a cytoprotective autophagy presumably through mTOR inhibition, which could be overcome by the cotreatment with the autophagy inhibitor chloroquine. Together, the ability of DMC to modulate multiple PPAR gamma -targeted signaling pathways provides a mechanistic basis to account for the antitumor activity of wild bitter melon.

[949]

TÍTULO / TITLE: - Treatment of Non-small Cell Lung Carcinoma after Failure of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Res. 2013 Jun;45(2):79-85. doi: 10.1158/1078-0432.CCR.12.279. Epub 2013 Jun 30.
<http://cancerres.aacrjournals.org/> ●● Cancer Research: <> Treat. 2013 Jun;45(2):79-85. doi: 10.1158/1078-0432.CCR.12.279. Epub 2013 Jun 30.

●● Enlace al texto completo (gratis o de pago) [4143/crt.2013.45.2.79](http://cancerres.aacrjournals.org/10.1158/1078-0432.CCR.12.279)

AUTORES / AUTHORS: - Lee JC; Jang SH; Lee KY; Kim YC

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

RESUMEN / SUMMARY: - Since the first description of non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutation as a distinct clinical entity, studies have proved EGFR tyrosine kinase inhibitors (TKIs) as a first choice of treatment. The median response duration of TKIs as a first-line treatment for EGFR mutant tumors ranges from 11 to 14 months. However, acquired resistance to EGFR-TKIs is inevitable due to various mechanisms, such as T790M, c-Met amplification, activation of alternative pathways (IGF-1, HGF, PI3CA, AXL), transformation to mesenchymal cell or small cell features, and tumor heterogeneity. Until development of a successful treatment strategy to overcome such acquired resistance, few options are currently available. Here we provide a summary of the therapeutic options after failure of first line EGFR-TKI treatment for NSCLC.

10.1158/1078-0432.CCR.12.279 &&NONONO&& TATATAT - Cancer Res Treat -----
----- [950]

TÍTULO / TITLE: - Inhibition of inducible heat shock protein-70 (hsp72) enhances bortezomib-induced cell death in human bladder cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 18;8(7):e69509. doi: 10.1371/journal.pone.0069509. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0069509](http://journals.plosone.org/journal.pone.0069509)

AUTORES / AUTHORS: - Qi W; White MC; Choi W; Guo C; Dinney C; McConkey DJ; Siefker-Radtke A

INSTITUCIÓN / INSTITUTION: - Department of Urology, U. T. M. D. Anderson Cancer Center Houston, Texas, United States of America.

RESUMEN / SUMMARY: - The proteasome inhibitor bortezomib (Velcade) is a promising new agent for bladder cancer therapy, but inducible cytoprotective mechanisms may limit its potential efficacy. We used whole genome mRNA expression profiling to study the effects of bortezomib on stress-induced gene expression in a panel of human bladder cancer cell lines. Bortezomib induced strong upregulation of the inducible HSP70 isoforms HSPA1A and HSPA1B isoforms of Hsp72 in 253J B-V and SW780 (HSPA1A(high)) cells, but only induced the HSPA1B isoform in UM-UC10 and UM-UC13 (HSPA1A(low)) cells. Bortezomib stimulated the binding of heat shock factor-1 (HSF1) to the HSPA1A promoter in 253JB-V but not in UM-UC13 cells. Methylation-specific PCR revealed that the HSPA1A promoter was methylated in the HSPA1A(low) cell lines (UM-UC10 and UM-UC13), and exposure to the chromatin demethylating agent 5-aza-2'-deoxycytidine restored HSPA1A expression. Overexpression of Hsp72 promoted bortezomib resistance in the UM-UC10 and UM-UC13 cells, whereas transient knockdown of HSPA1B further sensitized these cells to bortezomib, and exposure to the chemical HSF1 inhibitor KNK-437 promoted bortezomib sensitivity in the 253J B-V cells. Finally, shRNA-mediated stable knockdown of Hsp72 in 253J B-V promoted sensitivity to bortezomib in vitro and in tumor xenografts in vivo. Together, our results provide proof-of-concept for using Hsp72 inhibitors to promote bortezomib sensitivity in bladder cancers and suggest that selective targeting of HSPA1B could produce synthetic lethality in tumors that display HSPA1A promoter methylation.

[951]

TÍTULO / TITLE: - Co-treatment with Quercetin and 1,2,3,4,6-Penta-O-galloyl-beta-d-glucose Causes Cell Cycle Arrest and Apoptosis in Human Breast Cancer MDA-MB-231 and AU565 Cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Agric Food Chem. 2013 Jul 3;61(26):6430-45. doi: 10.1021/jf305253m. Epub 2013 Jun 19.

●● Enlace al texto completo (gratis o de pago) [1021/jf305253m](#)

AUTORES / AUTHORS: - Huang C; Lee SY; Lin CL; Tu TH; Chen LH; Chen YJ; Huang HC

INSTITUCIÓN / INSTITUTION: - National Research Institute of Chinese Medicine , Taipei 11221, Taiwan.

RESUMEN / SUMMARY: - Breast cancer is the most universal cancer in women, but the medications for breast cancer usually cause serious side effects and offer no effective treatment for triple-negative breast cancer. Here, we investigated the growth inhibitory effects of gallic acid (GA), (-)-epigallocatechin gallate (EGCG), or 1,2,3,4,6-penta-O-galloyl-beta-d-glucose (5GG) combined with quercetin (Que) on breast cancer cells. In this study, we tested the combined effects of these compounds on estrogen receptor (ER)/human epidermal growth factor 2 (Her2)-negative (MDA-MB-231), ER-positive/Her2-negative (BT483), and ER-negative/Her2-positive (AU565) breast cancer cells.

After treatment of each cell line with these compounds, we found that Que combined with 5GG induced S-phase arrest and apoptosis in MDA-BM-231 cells through downregulation of S-phase kinase protein 2 expression, but induced G2/M-phase arrest and apoptosis in AU565 cells through downregulation of Her2 expression. Additionally, Que combined with 5GG was more effective in inhibiting MDA-MB-231 cell growth than Que combined with EGCG (5GG analogue) or GA. The combination of 5GG and Que can offer great potential for the chemoprevention of ER-negative breast cancer.

[952]

TÍTULO / TITLE: - Ethyl acetate extract of germinated brown rice attenuates hydrogen peroxide-induced oxidative stress in human SH-SY5Y neuroblastoma cells: role of anti-apoptotic, pro-survival and antioxidant genes.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Jul 17;13:177. doi: 10.1186/1472-6882-13-177.

●● Enlace al texto completo (gratis o de pago) [1186/1472-6882-13-177](#)

AUTORES / AUTHORS: - Azmi NH; Ismail N; Imam MU; Ismail M

INSTITUCIÓN / INSTITUTION: - Laboratory of Molecular Biomedicine, Institute of Bioscience, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia. maznah@medic.upm.edu.my.

RESUMEN / SUMMARY: - BACKGROUND: There are reports of improved metabolic outcomes due to consumption of germinated brown rice (GBR). Many of the functional effects of GBR can be linked to its high amounts of antioxidants. Interestingly, dietary components with high antioxidants have shown promise in the prevention of neurodegenerative diseases like Alzheimer's disease (AD). This effect of dietary components is mostly based on their ability to prevent apoptosis, which is believed to link oxidative damage to pathological changes in AD. In view of the rich antioxidant content of GBR, we studied its potential to modulate processes leading up to AD. METHODS: The total phenolic content and antioxidant capacity of the ethyl acetate extract of GBR were compared to that of brown rice (BR), and the cytotoxicity of both extracts were determined on human SH-SY5Y neuronal cells using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) Assay. Based on its higher antioxidant potentials, the effect of the GBR extract on morphological changes due to hydrogen peroxide (H₂O₂)-induced oxidative damage in human SH-SY5Y neuronal cells was examined using inverted light microscope and fluorescence microscope by means of acridine orange-propidium iodide (AO/PI) staining. Also, evaluation of the transcriptional regulation of antioxidant and apoptotic genes was carried out using Multiplex Gene Expression System. RESULTS: The ethyl acetate extract of GBR had higher total phenolic content and antioxidant capacity compared to BR. The cytotoxicity results showed that GBR extract did not cause any damage to the human SH-SY5Y neuronal cells

at concentrations of up to 20 ppm, and the morphological analyses showed that the GBR extract (up to 10 ppm) prevented H₂O₂-induced apoptotic changes in the cells. Furthermore, multiplex gene expression analyses showed that the protection of the cells by the GBR extract was linked to its ability to induce transcriptional changes in antioxidant (SOD 1, SOD 2 and catalase) and apoptotic (AKT, NF-Kbeta, ERK1/2, JNK, p53 and p38 MAPK) genes that tended towards survival. CONCLUSIONS: Taken together, the results of our study showed that the ethyl acetate extract of GBR, with high antioxidant potentials, could prevent H₂O₂-induced oxidative damage in SH-SY5Y cells. The potential of GBR and its neuroprotective mechanism in ameliorating oxidative stress-related cytotoxicity is therefore worth exploring further.

[953]

TÍTULO / TITLE: - Prognostic Significance of alpha5beta1-integrin Expression in Cervical Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(6):3891-5.

AUTORES / AUTHORS: - Wang HY; Chen Z; Wang ZH; Wang H; Huang LM

INSTITUCIÓN / INSTITUTION: - Department of Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China E-mail : xiexianmu2008@126.com.

RESUMEN / SUMMARY: - The purpose of this study was to evaluate the association of expression of alpha5beta1-integrin with clinicopathologic features and prognosis in cervical cancer. Levels of alpha5beta1-integrin in normal cervical mucosa and cervical cancer tissue were detected with immunohistochemistry. Survival analysis by the Kaplan-Meier method was performed to assess prognostic significance. alpha5beta1-integrin expression was detected in 84.6% (143/169) cervical cancer samples, significantly different from that in normal cervical mucosa (P < 0.05). Positive expression rates of alpha5beta1-integrin in patients with poor histologic differentiation, lymph node metastasis, and recurrence were elevated. Using Kaplan-Meier analysis, a comparison of survival curves of low versus high expression of alpha5beta1-integrin revealed a highly significant difference in human cervical cancer cases (P < 0.05), suggesting that overexpression of alpha5beta1-integrin is associated with a worse prognosis. The alpha5beta1-integrin promotes angiogenesis and associates with lymph node metastasis, vascular invasion and poor prognosis of cervical cancer. The current study indicated that alpha5beta1-integrin may be an independent prognostic factor for cervical cancer patients.

[954]

TÍTULO / TITLE: - An apolipoprotein A-I mimetic targets scavenger receptor A on tumor-associated macrophages: A prospective anticancer treatment?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncoimmunology. 2013 Jun 1;2(6):e24461. Epub 2013 May 13.

●● Enlace al texto completo (gratis o de pago) 4161/onci.24461

AUTORES / AUTHORS: - Neyen C; Mukhopadhyay S; Gordon S; Hagemann T

INSTITUCIÓN / INSTITUTION: - Sir William Dunn School of Pathology; University of Oxford; Oxford, UK.

RESUMEN / SUMMARY: - Tumor-associated macrophages polarize toward an M2 phenotype and express scavenger receptor A (SRA), hence promoting tumor progression. We demonstrated that SRA can be therapeutically targeted in vivo with the small peptide inhibitor 4F to prevent metastatic spread. Beyond our study, 4F is emerging as a promising anticancer agent.

[955]

TÍTULO / TITLE: - NDST4 Is a Novel Candidate Tumor Suppressor Gene at Chromosome 4q26 and Its Genetic Loss Predicts Adverse Prognosis in Colorectal Cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 25;8(6):e67040. doi: 10.1371/journal.pone.0067040. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0067040

AUTORES / AUTHORS: - Tzeng ST; Tsai MH; Chen CL; Lee JX; Jao TM; Yu SL; Yen SJ; Yang YC

INSTITUCIÓN / INSTITUTION: - Department of Clinical Laboratory Sciences and Medical Biotechnology, College of Medicine, National Taiwan University, Taipei, Taiwan.

RESUMEN / SUMMARY: - BACKGROUND: Genomic deletion at tumor suppressor loci is a common genetic aberration in human cancers. The study aimed to explore candidate tumor suppressor genes at chromosome 4q25-q28.2 and to delineate novel prognostic biomarkers associated with colorectal cancer (CRC). METHODS: Deletion mapping of chromosome 4q25-q28.2 was conducted in 114 sporadic CRC by loss of heterozygosity study with 11 microsatellite markers. A novel candidate tumor suppressor gene, namely NDST4, was identified at 4q26. Gene expression of NDST4 was investigated in 52 pairs of primary CRC tissues by quantitative reverse transcription-polymerase chain reaction. Allelic loss of NDST4 gene was further determined in 174 colorectal carcinomas by loss of heterozygosity analysis, and then was assessed for clinical relevance. RESULTS: One minimal deletion region was delineated between D4S2297 and D4S2303 loci at 4q26, where NDST4 was the only gene that had markedly been downregulated in CRC tumors. By laser capture microdissection, NDST4 RNA expression was demonstrated in colonic epithelial cells, but was undetectable in tumor cells. In total, 30 (57.7%) of 52 colorectal carcinomas showed a dramatic reduction in NDST4 gene expression compared with matched normal mucosae. The genetic loss of NDST4 was significantly

associated with advanced pathological stage ($P = 0.039$) and poorer overall survival of patients ($P = 0.036$). CONCLUSIONS: NDST4 gene is a novel candidate tumor suppressor gene in human cancer, and the loss of its function might be involved in CRC progression. In addition, the loss of heterozygosity assay, which was established to determine the allelic loss of NDST4 gene, could be a cost-effective tool for providing a useful biomarker of adverse prognosis in CRC.

[956]

TÍTULO / TITLE: - Emodin induces apoptosis of human cervical cancer hela cells via intrinsic mitochondrial and extrinsic death receptor pathway.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cancer Cell Int. 2013 Jul 16;13(1):71. doi: 10.1186/1475-2867-13-71.

●● Enlace al texto completo (gratis o de pago) [1186/1475-2867-13-71](#)

AUTORES / AUTHORS: - Yaoxian W; Hui Y; Yunyan Z; Yanqin L; Xin G; Xiaoke W
INSTITUCIÓN / INSTITUTION: - Department of Gynecology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Hapin Road, 150040, Haerbin, Heilongjiang Province, China. xiaoke.wu@aliyun.com.

RESUMEN / SUMMARY: - BACKGROUND: Emodin is a natural anthraquinone derivative isolated from the *Rheum palmatum* L. Aim: The aim of the present study was to investigate the effect of emodin on the apoptosis of the human cervical cancer line HeLa and to identify the mechanisms involved. METHODS: Relative cell viability was assessed by MTT assay after treatment with emodin. Cell apoptosis was detected with TUNEL, Hoechst 33342 staining and quantified with flow cytometry using annexin FITC-PI staining. RESULTS: The percentage of apoptotic cells was 0.8, 8.2, 22.1, and 43.7%, respectively. The mRNA levels of Caspase-9, -8 and -3 detected by Real-time PCR after treatment with emodin were significantly increased. Emodin increased the protein levels of Cytochrome c, Apaf-1, Fas, FasL, and FADD but decreased the protein levels of Pro-caspase-9, Pro-caspase-8 and Pro-caspase-3. CONCLUSION: We conclude that the emodin inhibited HeLa proliferation by inducing apoptosis through the intrinsic mitochondrial and extrinsic death receptor pathways.

[957]

TÍTULO / TITLE: - Interferon alpha may be back on track to treat acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncoimmunology. 2013 Apr 1;2(4):e23619.

●● Enlace al texto completo (gratis o de pago) [4161/onci.23619](#)

AUTORES / AUTHORS: - Smits EL; Anguille S; Berneman ZN

INSTITUCIÓN / INSTITUTION: - Tumor Immunology Group, Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute, Faculty of

Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium ;
Center for Cell Therapy and Regenerative Medicine, Antwerp University
Hospital, Antwerp, Belgium.

RESUMEN / SUMMARY: - Our own experience and a thorough literature review suggest that interferon alpha (IFNalpha) should be reconsidered for the treatment of acute myeloid leukemia patients. Most likely, the success of such treatment depends on the achievement of high serum levels of IFNalpha for several months, which can be obtained by using pegylated IFNalpha.

[958]

TÍTULO / TITLE: - Human epidermal growth factor receptor 2-positive breast cancer: which cytotoxic agent best complements trastuzumab's efficacy in vitro?

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Jun 17;6:693-701. doi: 10.2147/OTT.S46883. Print 2013.

●● Enlace al texto completo (gratis o de pago) [2147/OTT.S46883](#)

AUTORES / AUTHORS: - Hurrell T; Outhoff K

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, University of Pretoria, Pretoria, South Africa.

RESUMEN / SUMMARY: - INTRODUCTION: Despite trastuzumab having enhanced selectivity for human epidermal growth factor receptor 2 (HER-2) overexpressing breast cancer cells, treatment is hampered by interindividual variation and tumors with high mitogenic potential. The lack of significant clinical benefit in certain patient cohorts suggests that HER-2 expression is ineffective as a sole prognostic indicator of response to therapy. Therefore, optimizing the clinical role of trastuzumab in drug combinations remains critical for clinical success. AIM: To investigate the effects of trastuzumab in combination with either doxorubicin or geldanamycin on in vitro cell viability, cell cycling, apoptosis and relative HER-2 expression in HER-2-positive (SK-BR-3) and estrogen receptor-positive (MCF-7) breast adenocarcinoma models. RESULTS: HER-2-rich SK-BR-3 cells demonstrated a greater sensitivity to the effects of doxorubicin than MCF-7 cells. Concurrent trastuzumab exposure resulted in a further reduction in cell viability. This decreased cell viability induced by doxorubicin was associated with activation of executioner caspases as well as with alterations in cell-cycle kinetics, primarily promoting S-phase accumulation. Doxorubicin had no effect on surface HER-2 density expression. Geldanamycin reduced cell viability significantly greater in SK-BR-3 than MCF-7 cells, and was associated with G2 cell-cycle accumulation. The addition of trastuzumab did not augment these effects. Geldanamycin promoted substantial reductions in relative surface HER-2 density in SK-BR-3 cells. CONCLUSION: The in vitro data supported the rationale for using doxorubicin in trastuzumab-based therapies. Therefore, despite the incidence of cardiotoxicity, doxorubicin could retain a fundamental role in treating HER-2-positive breast cancer. While

geldanamycin is a potent cytotoxic agent, its concurrent use with trastuzumab requires further research into the transient or permanent nature of alterations in HER-2 status in cell progeny.

[959]

TÍTULO / TITLE: - Induction of apoptosis and inhibition of angiogenesis by PEGylated liposomal quercetin in both cisplatin-sensitive and cisplatin-resistant ovarian cancers.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Biomed Nanotechnol. 2013 Jun;9(6):965-75.

AUTORES / AUTHORS: - Long Q; Xiel Y; Huang Y; Wu Q; Zhang H; Xiong S; Liu Y; Chen L; Wei Y; Zhao X; Gong C

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Biotherapy, West China Hospital, and Department of Gynecology and Obstetrics, Second West China Hospital, Sichuan University, Chengdu 610041, China.

RESUMEN / SUMMARY: - The clinical efficiency of cisplatin against ovarian cancer is often limited by the development of drug resistance. In this work, we investigated PEGylated liposomal quercetin (Lipo-Que) on cisplatin-sensitive (A2780s) and cisplatin-resistant (A2780cp) human ovarian cancer models in vitro and in vivo to reveal whether a cisplatin-resistant ovarian cancer has susceptibility to quercetin (Que) and the mechanism of its antitumor activity. Lipo-Que was prepared using a solid dispersion method, and the obtained Lipo-Que is monodisperse with a mean diameter of 163 +/-10 nm. Besides, in vitro drug release assay showed a sustained release behavior of Lipo-Que. In vitro experiments suggested that Lipo-Que inhibited cell proliferation, induced apoptosis, and induced cell cycle arrest in both A2780s and A2780cp cells. Furthermore, antitumor activity of Lipo-Que was investigated in both cisplatin-sensitive and cisplatin-resistant human ovarian tumor xenograft models in nude mice. Lipo-Que significantly suppressed tumor growth in both models in comparison with free Que, blank liposomes (Lipo), or normal saline (NS). Furthermore, immunohistochemistry and immunofluorescence tests revealed that Lipo-Que induced apoptosis, decreased microvessel density, and inhibited proliferation of tumors in both A2780s and A2780cp tumor models. Therefore, our results suggest that Lipo-Que is an effective agent to inhibit tumor growth in both cisplatin-sensitive and cisplatin-resistant human ovarian cancers.

[960]

TÍTULO / TITLE: - Gene expression profiling of ampullary carcinomas classifies ampullary carcinomas into biliary-like and intestinal-like subtypes that are prognostic of outcome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 11;8(6):e65144. doi: 10.1371/journal.pone.0065144. Print 2013.

- Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0065144](https://doi.org/10.1371/journal.pone.0065144)

AUTORES / AUTHORS: - Overman MJ; Zhang J; Kopetz S; Davies M; Zhi-Qin J; Stemke-Hale K; Rummele P; Pilarsky C; Grutzmann R; Hamilton S; Hwang R; Abbruzzese JL; Varadhachary G; Broom B; Wang H

INSTITUCIÓN / INSTITUTION: - Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, United States of America.

RESUMEN / SUMMARY: - BACKGROUND: Adenocarcinomas of the ampulla of Vater are classified as biliary cancers, though the exact epithelium of origin for these cancers is not known. We sought to molecularly classify ampullary adenocarcinomas in comparison to known adenocarcinomas of the pancreas, bile duct, and duodenum by gene expression analysis. METHODS: We analyzed 32 fresh-frozen resected, untreated periampullary adenocarcinomas (8 pancreatic, 2 extrahepatic biliary, 8 duodenal, and 14 ampullary) using the Affymetrix U133 Plus 2.0 genome array. Unsupervised and supervised hierarchical clustering identified two subtypes of ampullary carcinomas that were molecularly and histologically characterized. RESULTS: Hierarchical clustering of periampullary carcinomas segregated ampullary carcinomas into two subgroups, which were distinctly different from pancreatic carcinomas. Non-pancreatic periampullary adenocarcinomas were segregated into two subgroups with differing prognoses: 5 year RFS (77% vs. 0%, $p = 0.007$) and 5 year OS (100% vs. 35%, $p = 0.005$). Unsupervised clustering analysis of the 14 ampullary samples also identified two subgroups: a good prognosis intestinal-like subgroup and a poor prognosis biliary-like subgroup with 5 year OS of 70% vs. 28%, $P = 0.09$. Expression of CK7+/CK20- but not CDX-2 correlated with these two subgroups. Activation of the AKT and MAPK pathways were both increased in the poor prognostic biliary-like subgroup. In an independent 80 patient ampullary validation dataset only histological subtype (intestinal vs. pancreaticobiliary) was significantly associated with OS in both univariate ($p = 0.006$) and multivariate analysis ($P = 0.04$). CONCLUSIONS: Gene expression analysis discriminated pancreatic adenocarcinomas from other periampullary carcinomas and identified two prognostically relevant subgroups of ampullary adenocarcinomas. Histological subtype was an independent prognostic factor in ampullary adenocarcinomas.

[961]

TÍTULO / TITLE: - Functional promoter -31G/C variant of Survivin gene predict prostate cancer susceptibility among Chinese: a case control study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jul 24;13(1):356.

- Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-356](https://doi.org/10.1186/1471-2407-13-356)

AUTORES / AUTHORS: - Chen J; Cui X; Zhou H; Qin C; Cao Q; Ju X; Li P; Cai H; Zhu J; Meng X; Wang M; Zhang Z; Shao P; Li J; Yin C

RESUMEN / SUMMARY: - BACKGROUND: Abnormal expression of Baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5, also called as survivin), a novel member of the inhibitor of apoptosis protein (IAP) family, has implications in many types of cancer and is considered as a new therapeutic target. We suppose that genetic variant rs9904341 in the 5[prime] UTR region of survivin gene may be associated with the development and progression of prostate cancer (PCa) in Chinese population. METHODS: TaqMan assay method was used to genotype the polymorphism in the hospital-based case—control analysis of 665 patients with PCa and 710 age-matched cancer-free controls. The genetic associations with the occurrence and progression of PCa were calculated by logistic regression. RESULTS: Our results indicated that compared with GG genotypes, there was a statistically significant increased risk of PCa associated with those with CC genotypes [odds ratios (ORs) = 1.57, 95%confidence intervals (CIs) = 1.17-2.13, P = 0.004]. Moreover, stratification analysis revealed that the association was more pronounced in subgroups of nondrinkers, nonsmokers and those without a family history of cancer (all P < 0.05). In addition, we observed that PSA \geq 20 was more frequent in patients carrying GC/CC genotypes than in those with a wild type genotype. CONCLUSION: The functional survivin rs9904341 genetic variant may have a substantial influence on the PCa susceptibility and evolution.

[962]

TÍTULO / TITLE: - Clinicopathological correlates and prognostic significance of KRAS mutation status in a pooled prospective cohort of epithelial ovarian cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Diagn Pathol. 2013 Jun 25;8:106. doi: 10.1186/1746-1596-8-106.

●● Enlace al texto completo (gratis o de pago) [1186/1746-1596-8-106](#)

AUTORES / AUTHORS: - Nodin B; Zendehtrokh N; Sundstrom M; Jirstrom K

INSTITUCIÓN / INSTITUTION: - Department of Clinical Sciences, Division of Pathology, Lund University, Skane University Hospital, Lund, Sweden.

bjorn.nodin@med.lu.se

RESUMEN / SUMMARY: - BACKGROUND: Activating KRAS mutations are common in ovarian carcinomas of low histological grade, less advanced clinical stage and mucinous histological subtype, and form part of the distinct molecular alterations associated with type I tumors in the dualistic model of ovarian carcinogenesis. Here, we investigated the occurrence, clinicopathological correlates and prognostic significance of specific KRAS mutations in tumours from 153 epithelial ovarian cancer (EOC) cases from a pooled, prospective cohort. METHODS: KRAS codon 12,13 and 61 mutations were analysed by pyrosequencing in tumours from 163 incident EOC cases in the Malmo Diet and Cancer Study and Malmo Preventive Project. Associations of mutational status with clinicopathological and molecular characteristics were assessed by

Pearson Chi Square test. Ovarian cancer-specific survival (OCSS) according to mutational status was explored by Kaplan-Meier analysis and Cox proportional hazards modelling. KRAS-mutation status was also analysed in 28 concomitantly sampled benign-appearing fallopian tubes. RESULTS: Seventeen (11.1%) EOC cases harboured mutations in the KRAS gene, all but one in codon 12, and one in codon 13. No KRAS mutations were found in codon 61 and all examined fallopian tubes were KRAS wild-type. KRAS mutation was significantly associated with lower grade ($p = 0.001$), mucinous histological subtype ($p = < 0.001$) and progesterone receptor expression ($p = 0.035$). Kaplan-Meier analysis revealed a significantly improved OCSS for patients with KRAS-mutated compared to KRAS wild-type tumours ($p = 0.015$). These associations were confirmed in unadjusted Cox regression analysis (HR = 2.51; 95% CI 1.17-5.42) but did not remain significant after adjustment for age, grade and clinical stage. The beneficial prognostic impact of KRAS mutation was only evident in tumours of low-intermediate differentiation grade ($p = 0.023$), and in a less advanced clinical stage ($p = 0.014$). Moreover, KRAS mutation was associated with a significantly improved OCSS in the subgroup of endometrioid carcinomas ($p = 0.012$). CONCLUSIONS: The results from this study confirm previously demonstrated associations of KRAS mutations with well-differentiated and mucinous ovarian carcinomas. Moreover, KRAS-mutated tumours had a significantly improved survival in unadjusted, but not adjusted, analysis. A finding that merits further study is the significant prognostic impact of KRAS mutation in endometrioid carcinomas, potentially indicating that response to Ras/Raf/MEK/ERK-targeting therapies may differ by histological subtype. VIRTUAL SLIDES: The virtual slide(s) for this article can be found here: <http://www.diagnosticpathology.diagnomx.eu/vs/1788330379100147>.

[963]

TÍTULO / TITLE: - Personalized medicine for cancer therapy: Lessons learned from tumor-associated antigens.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncoimmunology. 2013 Apr 1;2(4):e23433.

●● Enlace al texto completo (gratis o de pago) [4161/onci.23433](#)

AUTORES / AUTHORS: - Scanlon CS; D'Silva NJ

INSTITUCIÓN / INSTITUTION: - Department of Periodontics and Oral Medicine, School of Dentistry; University of Michigan; Ann Arbor, MI USA.

RESUMEN / SUMMARY: - Antibody signatures may become sophisticated screening tools for early diagnosis and the development of personalized anticancer treatments. We used biopanning to enrich the immune response of head and neck squamous cell carcinoma (HNSCC) patients. This method revealed a HNSCC-specific antibody signature and allowed for the discovery of a novel oncogene, L23.

[964]

TÍTULO / TITLE: - Glycovariant anti-CD37 monospecific protein therapeutic exhibits enhanced effector cell-mediated cytotoxicity against chronic and acute B cell malignancies.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - MAbs. 2013 Jun 7;5(5).

AUTORES / AUTHORS: - Rafiq S; Siadak A; Butchar JP; Cheney C; Lozanski G; Jacob NK; Lapalombella R; McGourty J; Moledor M; Lowe R; Setter B; Jones J; Flynn JM; Andritsos L; Devine S; Mo X; Jarjoura D; Tridandapani S; Algate P; Byrd JC; Muthusamy N

INSTITUCIÓN / INSTITUTION: - Integrated Biomedical Science Graduate Program; The Ohio State University; Columbus, OH USA; Division of Hematology, Department of Internal Medicine; The Ohio State University; Columbus, OH USA.

RESUMEN / SUMMARY: - TRU-016 is a SMIP™ (monospecific protein therapeutic) molecule against the tetraspanin transmembrane family protein CD37 that is currently in Phase 2 trials in Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL). In an attempt to enhance the ADCC function of SMIP-016, the chimeric version of TRU-016, SMIP-016 (GV) was engineered with a modification in a glycosylation site in the Fc domain. The wild-type and glycovariant SMIP proteins mediate comparable Type I antibody-like direct cytotoxicity in the presence of anti-human Fc crosslinker and show a similar tyrosine phosphorylation pattern post-treatment. However, NK cells stimulated with the SMIP-016 (GV) exhibit enhanced activation and release 3-fold more interferon-gamma compared with SMIP-016. SMIP-016 (GV) shows enhanced ADCC function against cells expressing CD37 with NK cell effectors derived from both normal and CLL-affected individuals. Enhanced ADCC is observed against CLL cells and is sustained at concentrations of SMIP-016 (GV) as low as 5E (-6) microg/mL on cells expressing minimal CD37 antigen. In support of the biological relevance of this, SMIP-016 (GV) mediates effective ADCC against primary acute lymphoblastic leukemia (ALL) cells with low surface expression of CD37. Collectively, these data suggest potential use of the novel therapeutic agent SMIP-016 (GV) with enhanced effector function for B cell malignancies, including CLL and ALL therapy.

[965]

TÍTULO / TITLE: - Digitoxin induces apoptosis in cancer cells by inhibiting nuclear factor of activated T-cells-driven c-MYC expression.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Carcinog. 2013 May 20;12:8. doi: 10.4103/1477-3163.112268. Print 2013.

●● Enlace al texto completo (gratis o de pago) [4103/1477-](#)

[3163.112268](#)

AUTORES / AUTHORS: - Yang QF; Dalgard CL; Eidelman O; Jozwik C; Pollard BS; Srivastava M; Pollard HB

INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Physiology, and Genetics, Uniformed Services University School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA.

RESUMEN / SUMMARY: - **BACKGROUND:** Cardiac glycosides such as digitoxin have been shown to directly cause apoptotic death of cancer cells both in vitro, and in vivo. However, the mechanism connecting cardiac glycoside action to apoptosis is not known. It has been reported that compounds resembling digitoxin are able to reduce c-MYC expression. Furthermore, it has been previously shown that the transcription of c-MYC depends on nuclear factor of activated T-cells (NFAT) binding sites in the c-MYC promoter. We have therefore hypothesized that NFAT might mediate digitoxin effects on c-MYC mRNA message. **MATERIALS AND METHODS:** We have chosen to study this process in HeLa cells where structurally intact c-MYC genes in 8q24 co-localize with human papilloma virus 18 at all integration sites. **RESULTS:** Here we show that within the 1(st) h following treatment with digitoxin, a significant reduction in c-MYC mRNA occurs. This is followed by a precipitous loss of c-MYC protein, activation of caspase 3, and subsequent apoptotic cell death. To test the NFAT-dependence mechanism, we analyzed the effects of digitoxin on NFAT isoform-dependent auto-activation of a NFAT-luciferase expression system. Drug dependent effects on expression varied according to each of the four canonical NFAT isoforms (1, 2, 3 or 4). The most digitoxin-sensitive NFAT isoform was NFAT1. Using c-MYC chromatin immune precipitation, we find that digitoxin inhibits interaction of NFAT1 with the proximal c-MYC promoter. **CONCLUSIONS:** These results suggest that the carcinotoxic activity of digitoxin includes suppression of NFAT-driven c-MYC expression.

[966]

TÍTULO / TITLE: - Calretinin mediates apoptosis in small cell lung cancer cells expressing tetraspanin CD9.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - FEBS Open Bio. 2013 May 10;3:225-30. doi: 10.1016/j.fob.2013.04.005. Print 2013.

●● Enlace al texto completo (gratis o de pago) [1016/j.fob.2013.04.005](https://doi.org/10.1016/j.fob.2013.04.005)

AUTORES / AUTHORS: - He P; Kuhara H; Tachibana I; Jin Y; Takeda Y; Tetsumoto S; Minami T; Kohmo S; Hirata H; Takahashi R; Inoue K; Nagatomo I; Kida H; Kijima T; Naka T; Morii E; Kawase I; Kumanogoh A

INSTITUCIÓN / INSTITUTION: - Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka 565-0871, Japan ; Department of Respiratory Medicine, The Second Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an 71004, China.

RESUMEN / SUMMARY: - A majority of small cell lung cancer (SCLC) cells lack a metastasis suppressor, tetraspanin CD9, and CD9 expression promotes their apoptosis. By a proteomics-based approach, we compared an SCLC cell line with its CD9 transfectant and found that a calcium-binding neuronal protein,

calretinin, is upregulated in CD9-positive SCLC cells. Ectopic or anticancer drug-induced CD9 expression upregulated calretinin, whereas CD9 knockdown down-regulated calretinin in SCLC cells. When calretinin was knocked down, CD9-positive SCLC cells revealed increased Akt phosphorylation and decreased apoptosis. These results suggest that CD9 positively regulates the expression of calretinin that mediates proapoptotic effect in SCLC cells.

[967]

TÍTULO / TITLE: - Stimulation of Toll-like receptor-1/2 combined with Velcade increases cytotoxicity to human multiple myeloma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Blood Cancer J. 2013 May 31;3:e119. doi: 10.1038/bcj.2013.17.

●● Enlace al texto completo (gratis o de pago) [1038/bcj.2013.17](#)

AUTORES / AUTHORS: - Abdi J; Mutis T; Garssen J; Redegeld F

INSTITUCIÓN / INSTITUTION: - Faculty of Science, Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.

RESUMEN / SUMMARY: - An increasing body of evidence supports the important role of adhesion to bone marrow microenvironment components for survival and drug resistance of multiple myeloma (MM) cells. Previous studies suggested that stimulation of Toll-like receptors by endogenous ligands released during inflammation and tissue damage may be pro-tumorigenic, but no studies have been performed in relation to modulation of cell adhesion and drug cytotoxicity. Here, we investigated the effect of TLR1/2 activation on adhesion of human myeloma cells to fibronectin, and their sensitivity to the proteasome inhibitor Velcade. It was found that TLR1/2 activation with Pam3CSK4 increased the cytotoxicity of Velcade in L363, OPM-2 and U266 human myeloma cells. This effect was not related to a decreased adhesion of the cells to fibronectin, but TLR1/2 activation stimulated the caspase-3 activity in Velcade-treated myeloma cells, which may be responsible for the enhanced cell death. Inhibitors of NF-kappaB and MAPK reduced the stimulatory effect. These findings indicate that TLR activation of MM cells could bypass protective effects of cell adhesion and suggest that TLR signaling may also have antitumorigenic potential.

[968]

TÍTULO / TITLE: - (-)-Epigallocatechin gallate inhibits the expression of indoleamine 2,3-dioxygenase in human colorectal cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2012 Sep;4(3):546-550. Epub 2012 Jun 15.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2012.761](#)

AUTORES / AUTHORS: - Ogawa K; Hara T; Shimizu M; Nagano J; Ohno T; Hoshi M; Ito H; Tsurumi H; Saito K; Seishima M; Moriwaki H

INSTITUCIÓN / INSTITUTION: - Department of Internal Medicine, Gifu University Graduate School of Medicine, Gifu 501-1194.

RESUMEN / SUMMARY: - Immune escape, the ability of tumor cells to avoid tumor-specific immune responses, occurs during the development and progression of several types of human malignancies, including colorectal cancer (CRC). Indoleamine 2,3-dioxygenase (IDO), the tryptophan catabolic enzyme, plays a significant role in regulating the immune response and provides tumor cells with a potent tool to evade the immune system. In the present study, we examined the effects of (-)-epigallocatechin gallate (EGCG), the major catechin in green tea, on the inhibition of IDO expression induced by interferon (IFN)-gamma in human CRC cells. We found that IFN-gamma increased the expression levels of IDO protein and mRNA in HT29 and SW837 CRC cell lines. Treatment of SW837 cells with EGCG significantly decreased IFN-gamma-induced expression of IDO protein and mRNA in a dose-dependent manner. Enzymatic activity of IDO, determined by the concentration of L-kynurenine in the culture medium, was also significantly inhibited by EGCG treatment. Phosphorylation of signal transducer and activator of transcription 1 (STAT1) induced by IFN-gamma was also significantly inhibited by EGCG. Reporter assays indicated that EGCG inhibited the transcriptional activities of IDO promoters, IFN-stimulated response element and IFN-gamma activation sequence, activated by STAT1 phosphorylation. These findings suggest that EGCG may exert antitumor effects on CRC, at least in part, by inhibiting the expression and function of IDO through the suppression of STAT1 activation. EGCG may, thus, serve as a potential agent for antitumor immunotherapy and be useful in the chemoprevention and/or treatment of CRC.

[969]

TÍTULO / TITLE: - Small molecule R1498 as a well-tolerated and orally active kinase inhibitor for hepatocellular carcinoma and gastric cancer treatment via targeting angiogenesis and mitosis pathways.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 5;8(6):e65264. doi: 10.1371/journal.pone.0065264. Print 2013.

●● Enlace al texto completo (gratis o de pago)

[1371/journal.pone.0065264](#)

AUTORES / AUTHORS: - Zhang C; Wu X; Zhang M; Zhu L; Zhao R; Xu D; Lin Z; Liang C; Chen T; Chen L; Ren Y; Zhang J; Qin N; Zhang X

INSTITUCIÓN / INSTITUTION: - Roche Research and Early Development China, Shanghai, China.

RESUMEN / SUMMARY: - Protein kinases play important roles in tumor development and progression. Lots of kinase inhibitors have entered into market and show promising clinical benefits. Here we report the discovery of a novel small molecule, well-tolerated, orally active kinase inhibitor, R1498, majorly targeting both angiogenic and mitotic pathways for the treatment of

hepatocellular carcinoma (HCC) and gastric cancer (GC). A series of biochemical and cell-based assays indicated that the target kinase cluster of R1498 included Aurora kinases and VEGFR2 et al. R1498 showed moderate in vitro growth inhibition on a panel of tumor cells with IC50 of micromole range. The in vivo anti-tumor efficacy of R1498 was evaluated on a panel of GC and HCC xenografts in a parallel comparison with another multikinase inhibitor sorafenib. R1498 demonstrated superior efficacy and toxicity profile over sorafenib in all test models with >80% tumor growth inhibition and tumor regression in some xenografts. The therapeutic potential of R1498 was also highlighted by its efficacy on three human GC primary tumor derived xenograft models with 10-30% tumor regression rate. R1498 was shown to actively inhibit the Aurora A activity in vivo, and decrease the vascularization in tumors. Furthermore, R1498 presented good in vivo exposure and therapeutic window in the pharmacokinetic and dose range finding studies. These evidences indicate that R1498 is a potent, well-tolerated, orally active multitarget kinase inhibitor with a unique antiangiogenic and antiproliferative profile, and provide strong confidence for further development for HCC and GC therapy.

[970]

TÍTULO / TITLE: - Increased coexpression of c-KIT and FLT3 receptors on myeloblasts: Independent predictor of poor outcome in pediatric acute myeloid leukemia.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cytometry B Clin Cytom. 2013 Jun 5:0. doi: 10.1002/cyto.b.21098.

●● Enlace al texto completo (gratis o de pago) [1002/cyto.b.21098](#)

AUTORES / AUTHORS: - Sharawat SK; Gupta R; Raina V; Kumar L; Sharma A; Iqbal S; Bakhshi R; Vishnubhatla S; Bakhshi S

INSTITUCIÓN / INSTITUTION: - Department of Medical Oncology, University of Delhi; Dr. B. R.A. Institute Rotary Cancer Hospital, New Delhi, India; All India Institute of Medical Sciences, New Delhi, India.

RESUMEN / SUMMARY: - BACKGROUND: Significance of mutations in FLT3 and c-KIT genes in AML has been well established, but role of their coexpression has not been evaluated. The aim of this study was to evaluate clinical significance of FLT3 (CD135) and c-KIT (CD117) coexpression on myeloblasts in AML. METHODS: Using flow-cytometry, we prospectively observed in 115 AML patients that CD135, CD117, and CD135+CD117 coexpression was expressed in 95 (82%), 104 (90%), and 81 (70%) patients respectively. Median expression of CD135, CD117, and their co expression was used as cut off for high and low expression. RESULTS: FLT3 ITD (internal tandem duplication) was present in 20 (17%) patients. High coexpression did not correlate with FLT3 ITD (P = 0.432) and cytogenetics (P = 0.244). Out of 115 patients, 86 (74.7%) achieved remission. At median followup of 15.5 months, EFS and OS was 29% and 35%, respectively for the entire cohort. Patients with high

coexpression of CD135 and CD117 in comparison to those with low coexpression had significantly inferior EFS (20% vs 38% $P < 0.001$) and OS (27% vs 44% $P = 0.001$). In step wise Cox regression multivariable analysis, hazard ratio for high hemoglobin, WBC count, and coexpression of CD135 and CD117 was 0.63, 1.73, and 2.46 respectively for EFS, and for OS only CD135+CD117 coexpression emerged as an independent predictor (hazard ratio 2.25). CONCLUSIONS: This is the first study to show that high coexpression of CD135+CD117 is an independent predictor of poor outcome in AML and is easily measurable by routine diagnostic flow-cytometry. © 2013 International Clinical Cytometry Society.

[971]

TÍTULO / TITLE: - High dose of extracellular ATP switched autophagy to apoptosis in anchorage-dependent and anchorage-independent hepatoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Purinergic Signal. 2013 Jun 19.

- [Enlace al texto completo \(gratis o de pago\) 1007/s11302-013-9369-](#)

[0](#)

AUTORES / AUTHORS: - Wei Q; Zhang Y; Sun L; Jia X; Huai W; Yu C; Wan Z; Han L

INSTITUCIÓN / INSTITUTION: - Department of Immunology, Shandong Provincial Key Laboratory of Infection & Immunology, School of Medicine, Shandong University, 44 West Wenhua Road, Jinan, 250012, China.

RESUMEN / SUMMARY: - Extracellular adenosine triphosphate (eATP) transduces purinergic signal and plays an important regulatory role in many biological processes, including tumor cell growth and cell death. A large amount of eATP exists in the fast-growing tumor center and inflammatory tumor microenvironment. Tumor cells could acquire anoikis resistance and anchorage independence in tumor microenvironment and further cause metastatic lesion. Whether such a high amount of eATP has any effect on the anchored and non-anchored tumor cells in tumor microenvironment has not been elucidated and is investigated in this study. Our data showed that autophagy helped hepatoma cells to maintain survival under the treatment of no more than 1 mM of eATP. Only when eATP concentration reached a relatively high level (2.5 mM), cell organelle could not be further maintained by autophagy, and apoptosis and cell death occurred. In hepatoma cells under treatment of 2.5 mM of eATP, an AMP-activated protein kinase (AMPK) pathway was dramatically activated while mTOR signaling pathway was suppressed in coordination with apoptosis. Further investigation showed that the AMPK/mTOR axis played a key role in tipping the balance between autophagy-mediated cell survival and apoptosis-induced cell death under the treatment of eATP. This work provides evidence to explain how hepatoma cells escape from eATP-induced cytotoxicity as well as offers an important clue to consider effective manipulation of cancer.

[972]

TÍTULO / TITLE: - Correlation between Beta1 integrin expression and prognosis in clinically localized prostate cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Int Braz J Urol. 2013 May-Jun;39(3):335-43. doi: 10.1590/S1677-5538.IBJU.2013.03.06.

AUTORES / AUTHORS: - Pontes-Junior J; Reis ST; Bernardes FS; Oliveira LC; de Barros EA; Dall'oglio MF; Timosczyk LM; Ribeiro-Filho LA; Srougi M; Leite KR

INSTITUCIÓN / INSTITUTION: - Laboratory of Medical Investigation - LIM 55, Urology Department, University of Sao Paulo Medical, School and Universidade Nove de Julho, Sao Paulo, Brazil.

RESUMEN / SUMMARY: - Integrins are transmembrane glycoprotein receptors that regulate cell-matrix interactions, thus functioning as sensors from the environment. They also act as cell adhesion molecules that are responsible for the maintenance of the normal epithelial phenotype. Some studies have reported a correlation between carcinogenesis and changes in integrin expression, especially beta1 integrin, however its role in prostate cancer (PC) is unclear. The aim of our study was to evaluate the expression of beta1 integrin in localized PC and to correlate the pattern of expression with recurrence after surgical treatment. Methods For this case-control study, we retrospectively selected surgical specimens from 111 patients with localized PC who underwent radical prostatectomy. Recurrence was defined as a PSA level exceeding 0.2ng/mL after surgery, and the median follow-up was 123 months. Integrin expression was evaluated by immunohistochemistry in a tissue microarray containing two samples from each tumor. We employed a semiquantitative analysis and considered a case as positive when the expression was strong and diffusely present. Results: There was a loss of 11 cases during the tissue micro array assembling. beta1 expression was positive in 79 of the 100 evaluated cases (79%). The univariate and multivariate analyses showed that the negative expression of beta1 integrin was associated with biochemical recurrence ($p = 0.047$) and time to recurrence after radical prostatectomy ($p = 0.023$). When beta1 was negative, the odds ratio for recurrence was 2.78 times higher than that observed in the positive cases [OR = 2.78, $p = 0.047$, IC 95% (1.01-7.66)]. Conclusions: The loss of beta1 integrin immune expression was correlated with biochemical recurrence in patients treated with radical prostatectomy for localized PC.

[973]

TÍTULO / TITLE: - RNase non-sensitive and endocytosis independent siRNA delivery system: delivery of siRNA into tumor cells and high efficiency induction of apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nanoscale. 2013 Aug 21;5(16):7256-64. doi: 10.1039/c3nr01183f. Epub 2013 Jul 1.

●● Enlace al texto completo (gratis o de pago) [1039/c3nr01183f](https://doi.org/10.1039/c3nr01183f)

AUTORES / AUTHORS: - Jiang X; Wang G; Liu R; Wang Y; Wang Y; Qiu X; Gao X

INSTITUCIÓN / INSTITUTION: - Department of Anatomy, Key Laboratory of Construction and Detection of Guangdong Province, Southern Medical University, Guangzhou 510515, P.R. China. giuxzh@aliyun.com.

RESUMEN / SUMMARY: - To date, RNase degradation and endosome/lysosome trapping are still serious problems for siRNA-based molecular therapy, although different kinds of delivery formulations have been tried. In this report, a cell penetrating peptide (CPP, including a positively charged segment, a linear segment, and a hydrophobic segment) and a single wall carbon nanotube (SWCNT) are applied together by a simple method to act as a siRNA delivery system. The siRNAs first form a complex with the positively charged segment of CPP via electrostatic forces, and the siRNA-CPP further coats the surface of the SWCNT via hydrophobic interactions. This siRNA delivery system is non-sensitive to RNase and can avoid endosome/lysosome trapping in vitro. When this siRNA delivery system is studied in Hela cells, siRNA uptake was observed in 98% Hela cells, and over 70% mRNA of mammalian target of rapamycin (mTOR) is knocked down, triggering cell apoptosis on a significant scale. Our siRNA delivery system is easy to handle and benign to cultured cells, providing a very efficient approach for the delivery of siRNA into the cell cytosol and cleaving the target mRNA therein.

[974]

TÍTULO / TITLE: - Oral cancer prognosis based on clinicopathologic and genomic markers using a hybrid of feature selection and machine learning methods.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Bioinformatics. 2013 May 31;14:170. doi: 10.1186/1471-2105-14-170.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2105-14-170](https://doi.org/10.1186/1471-2105-14-170)

AUTORES / AUTHORS: - Chang SW; Abdul-Kareem S; Merican AF; Zain RB

INSTITUCIÓN / INSTITUTION: - Bioinformatics and Computational Biology, Institute of Biological Science, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia. changsiowwee@yahoo.com

RESUMEN / SUMMARY: - BACKGROUND: Machine learning techniques are becoming useful as an alternative approach to conventional medical diagnosis or prognosis as they are good for handling noisy and incomplete data, and significant results can be attained despite a small sample size. Traditionally, clinicians make prognostic decisions based on clinicopathologic markers. However, it is not easy for the most skilful clinician to come out with an accurate prognosis by using these markers alone. Thus, there is a need to use genomic markers to improve the accuracy of prognosis. The main aim of this

research is to apply a hybrid of feature selection and machine learning methods in oral cancer prognosis based on the parameters of the correlation of clinicopathologic and genomic markers. RESULTS: In the first stage of this research, five feature selection methods have been proposed and experimented on the oral cancer prognosis dataset. In the second stage, the model with the features selected from each feature selection methods are tested on the proposed classifiers. Four types of classifiers are chosen; these are namely, ANFIS, artificial neural network, support vector machine and logistic regression. A k-fold cross-validation is implemented on all types of classifiers due to the small sample size. The hybrid model of ReliefF-GA-ANFIS with 3-input features of drink, invasion and p63 achieved the best accuracy (accuracy = 93.81%; AUC = 0.90) for the oral cancer prognosis. CONCLUSIONS: The results revealed that the prognosis is superior with the presence of both clinicopathologic and genomic markers. The selected features can be investigated further to validate the potential of becoming as significant prognostic signature in the oral cancer studies.

[975]

TÍTULO / TITLE: - Response Prediction to Neoadjuvant Chemotherapy: Comparison between Pre-Therapeutic Gene Expression Profiles and In Vitro Chemosensitivity Assay.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 24;8(6):e66573. doi: 10.1371/journal.pone.0066573. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0066573

AUTORES / AUTHORS: - Singer CF; Klingmuller F; Stratmann R; Staudigl C; Fink-Retter A; Gschwantler D; Helmy S; Pfeiler G; Dressler AC; Sartori C; Bilban M

INSTITUCIÓN / INSTITUTION: - Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.

RESUMEN / SUMMARY: - Although the use of (neo-)adjuvant chemotherapy in breast cancer patients has resulted in improved outcome, not all patients benefit equally. We have evaluated the utility of an in vitro chemosensitivity assay in predicting response to neoadjuvant chemotherapy. Pre-therapeutic biopsies were obtained from 30 breast cancer patients assigned to neoadjuvant epirubicin 75 mg/m² and docetaxel 75 mg/m² (Epi/Doc) in a prospectively randomized clinical trial. Biopsies were subjected to a standardized ATP-based Epi/Doc chemosensitivity assay, and to gene expression profiling. Patients then received 3 cycles of chemotherapy, and response was evaluated by changes in tumor diameter and Ki67 expression. The efficacy of Epi/Doc in vitro was correlated with differential changes in tumor cell proliferation in response to Epi/Doc in vivo ($p = 0.0011$; $r = 0.73670$, Spearman's rho), but did not predict for changes in tumor size. While a pre-therapeutic gene expression signature

identified tumors with a clinical response to Epi/Doc, no such signature could be found for tumors that responded to Epi/Doc in vitro, or tumors in which Epi/Doc exerted an antiproliferative effect in vivo. This is the first prospective clinical trial to demonstrate the utility of a standardized in vitro chemosensitivity assay in predicting the individual biological response to chemotherapy in breast cancer.

[976]

TÍTULO / TITLE: - Yin yang gene expression ratio signature for lung cancer prognosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jul 17;8(7):e68742. doi: 10.1371/journal.pone.0068742. Print 2013.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[1371/journal.pone.0068742](#)

AUTORES / AUTHORS: - Xu W; Banerji S; Davie JR; Kassie F; Yee D; Kratzke R

INSTITUCIÓN / INSTITUTION: - Manitoba Institute of Cell Biology, University of Manitoba, Winnipeg, Canada ; Manitoba Institute of Child Health, University of Manitoba, Winnipeg, Canada ; Faculty of Pharmacy, University of Manitoba, Winnipeg, Canada.

RESUMEN / SUMMARY: - Many studies have established gene expression-based prognostic signatures for lung cancer. All of these signatures were built from training data sets by learning the correlation of gene expression with the patients' survival time. They require all new sample data to be normalized to the training data, ultimately resulting in common problems of low reproducibility and impracticality. To overcome these problems, we propose a new signature model which does not involve data training. We hypothesize that the imbalance of two opposing effects in lung cancer cells, represented by Yin and Yang genes, determines a patient's prognosis. We selected the Yin and Yang genes by comparing expression data from normal lung and lung cancer tissue samples using both unsupervised clustering and pathways analyses. We calculated the Yin and Yang gene expression mean ratio (YMR) as patient risk scores. Thirty-one Yin and thirty-two Yang genes were identified and selected for the signature development. In normal lung tissues, the YMR is less than 1.0; in lung cancer cases, the YMR is greater than 1.0. The YMR was tested for lung cancer prognosis prediction in four independent data sets and it significantly stratified patients into high- and low-risk survival groups ($p = 0.02$, HR = 2.72; $p = 0.01$, HR = 2.70; $p = 0.007$, HR = 2.73; $p = 0.005$, HR = 2.63). It also showed prediction of the chemotherapy outcomes for stage II & III. In multivariate analysis, the YMR risk factor was more successful at predicting clinical outcomes than other commonly used clinical factors, with the exception of tumor stage. The YMR can be measured in an individual patient in the clinic independent of gene expression platform. This study provided a novel insight into the biology of lung cancer and shed light on the clinical applicability.

[977]

TÍTULO / TITLE: - Prognostic value of pretreatment carcinoembryonic antigen level on tumour downstaging and early occurring metastasis in locally advanced rectal cancer following 30gy/10f neoadjuvant radiotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Colorectal Dis. 2013 Jul 15. doi: 10.1111/codi.12354.

●● [Enlace al texto completo \(gratis o de pago\) 1111/codi.12354](#)

AUTORES / AUTHORS: - Wang L; Zhong XG; Peng YF; Li ZW; Gu J

INSTITUCIÓN / INSTITUTION: - Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Colorectal Surgery, Peking University Cancer Hospital & Institute.

RESUMEN / SUMMARY: - AIM: To evaluate the role of carcinoembryonic antigen (CEA) in predicting response to and prognosis for locally advanced rectal cancer treated with 30gy/10f neoadjuvant radiotherapy (nRT). METHODS: This retrospective study involved 240 patients with locally advanced rectal cancer who underwent 30gy/10f nRT (BED: 36Gy) followed by total mesorectal excision (TME) between August 2003 and August 2009. Serum CEA level was determined before nRT administration. The prognostic value of serum CEA level on tumor downstaging and 3 year disease-free survival were analyzed. RESULTS: Ninety out of 240 (37.5%) patients had elevated CEA levels before nRT. The incidence of T downstaging in patients decreased significantly as the pretreatment CEA levels became more elevated (<5ng/ml, 50.7%; 5-10ng/ml, 39.5%; >10ng/ml, 17.3%; P= 0.000). Downstaging to ypCR or ypStage I occurred in 46.7% (66/150) of patients with CEA level <5ng/ml and 34.2% (13/38) of patients with CEA level 5-10ng/ml. In contrast, merely 13.5% (7/52) of those with CEA level >10ng/ml downstaged to ypStage I and none of them achieved ypCR, with statistically difference (p=0.001). A significantly higher incidence of early metastasis (within 6 postoperative months) was observed with increasing CEA level: 2.0% (3/150), 5.4% (2/38) and 11.5% (6/52) in patients with CEA level <5ng/ml, 5-10ng/ml or >10ng/ml respectively (P = 0.018). CONCLUSION: Pretreatment CEA level cannot only predict tumour downstaging and ypTNM stage for rectal cancer following 30Gy/10f nRT, but also promisingly suggests a high incidence of early occurring distant metastasis. These findings may be used to select patients with nRT resistance and occult metastasis and make alternative treatment strategies. This article is protected by copyright. All rights reserved.

[978]

TÍTULO / TITLE: - RUNX3 gene promoter demethylation by 5-Aza-CdR induces apoptosis in breast cancer MCF-7 cell line.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Onco Targets Ther. 2013 Apr 17;6:411-7. doi: 10.2147/OTT.S43744. Print 2013.

●● Enlace al texto completo (gratis o de pago) 2147/OTT.S43744

AUTORES / AUTHORS: - Kang HF; Dai ZJ; Bai HP; Lu WF; Ma XB; Bao X; Lin S; Wang XJ

INSTITUCIÓN / INSTITUTION: - Department of Oncology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, People's Republic of China.

RESUMEN / SUMMARY: - Runt-related transcription factor 3 (RUNX3) is a tumor suppressor gene, its inactivation due to hypermethylation related to carcinogenesis. The aim of this study was to investigate the effects of 5-aza-2'-deoxycytidine (5-Aza-CdR) on cell proliferation and apoptosis by demethylation of the promoter region and restoring the expression of RUNX3 in the breast cancer MCF-7 cell line. MCF-7 cells were cultured with different concentrations (0.4-102.4 $\mu\text{mol/L}$) of 5-Aza-CdR in vitro. MTT assay was used to determine the proliferation of MCF-7 cells. Flow cytometry and Hoechst staining were used for analyzing cell apoptosis. The methylation status and expression of RUNX3 in mRNA and protein levels were measured by methylation-specific polymerase chain reaction (PCR [MSP]), reverse transcription (RT)-PCR, and Western blot. It was shown that the RUNX3 gene downregulated and hypermethylated in MCF-7 cells. 5-Aza-CdR induced demethylation, upregulated the expression of RUNX3 on both mRNA and protein levels in cancer cells, and induced growth suppression and apoptosis in vitro in a dose- and time-dependent manner. The results demonstrate that RUNX3 downregulation in breast cancer is frequently due to hypermethylation, and that 5-Aza-CdR can inhibit cell proliferation and induce apoptosis by eliminating the methylation status of RUNX3 promoter and restoring its expression.

[979]

TÍTULO / TITLE: - ER stress-mediated apoptosis induced by celastrol in cancer cells and important role of glycogen synthase kinase-3 β in the signal network.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Jul 11;4:e715. doi: 10.1038/cddis.2013.222.

●● Enlace al texto completo (gratis o de pago) 1038/cddis.2013.222

AUTORES / AUTHORS: - Feng L; Zhang D; Fan C; Ma C; Yang W; Meng Y; Wu W; Guan S; Jiang B; Yang M; Liu X; Guo D

INSTITUCIÓN / INSTITUTION: - Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China.

RESUMEN / SUMMARY: - HeLa cells treated with celastrol, a natural compound with inhibitive effect on proteasome, exhibited increase in apoptotic rate and characteristics of apoptosis. To clarify the signal network activated by celastrol to induce apoptosis, both the direct target proteins and indirect target proteins of celastrol were searched in the present study. Proteasome catalytic subunit beta1 was predicted by computational analysis to be a possible direct target of celastrol and confirmed by checking direct effect of celastrol on the activity of

recombinant human proteasome subunit beta1 in vitro. Undirect target-related proteins of celastrol were searched using proteomic studies including two-dimensional electrophoresis (2-DE) analysis and iTRAQ-based LC-MS analysis. Possible target-related proteins of celastrol such as endoplasmic reticulum protein 29 (ERP29) and mitochondrial import receptor Tom22 (TOM22) were found by 2-DE analysis of total cellular protein expression profiles. Further study showed that celastrol induced ER stress and ER stress inhibitor could ameliorate cell death induced by celastrol. Celastrol induced translocation of Bax into the mitochondria, which might be related to the upregulation of BH-3-only proteins such as BIM and the increase in the expression level of TOM22. To further search possible target-related proteins of celastrol in ER and ER-related fractions, iTRAQ-based LC-MS method was used to analyze protein expression profiles of ER/microsomal vesicles-riched fraction of cells with or without celastrol treatment. Based on possible target-related proteins found in both 2-DE analysis and iTRAQ-based LC-MS analysis, protein-protein interaction (PPI) network was established using bioinformatic analysis. The important role of glycogen synthase kinase-3beta (GSK3beta) in the signal cascades of celastrol was suggested. Pretreatment of LiCl, an inhibitor of GSK3beta, could significantly ameliorate apoptosis induced by celastrol. On the basis of the results of the present study, possible signal network of celastrol activated by celastrol leading to apoptosis was predicted.

[980]

TÍTULO / TITLE: - The interaction of sesamol with DNA and cytotoxicity, apoptosis, and localization in HepG2 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Food Chem. 2013 Nov 1;141(1):289-96. doi: 10.1016/j.foodchem.2013.02.105. Epub 2013 Mar 7.

●● Enlace al texto completo (gratis o de pago)

[1016/j.foodchem.2013.02.105](#)

AUTORES / AUTHORS: - Liu Z; Xiang Q; Du L; Song G; Wang Y; Liu X

INSTITUCIÓN / INSTITUTION: - College of Food Science and Engineering, Northwest A&F University, Yangling, China.

RESUMEN / SUMMARY: - Sesamol, a nutritional antioxidant phenolic compound present in sesame seed, has a potential therapeutic molecule effect against cancers. In this study, the interaction between sesamol and DNA was investigated by employing ultraviolet/visible (UV/Vis), fluorescence, circular dichroism (CD), Fourier transform infrared spectroscopy (FT-IR), and molecular modeling. The fluorescence analysis indicated that the fluorescence quenching mechanism of sesamol by calf thymus DNA (ctDNA) occurred through static quenching. The UV/Vis, CD, FT-IR spectra and molecular docking results implied that the primary binding mode was minor groove binding. Furthermore, the intracellular interaction of sesamol with DNA and its bioactivity effect were explored. The cell activity results demonstrated that sesamol induced hepatic

cell line (HepG2) death. The acridine orange (AO)/ethidium bromide (EB) staining assay and DNA fragmentation confirmed that sesamol could efficiently induce the apoptosis of HepG2 cells. Moreover, addition of sesamol to HepG2 cells resulted in nuclear localization, as visualized by confocal microscopy.

[981]

TÍTULO / TITLE: - Magnetic resonance imaging biomarkers in hepatocellular carcinoma: association with response and circulating biomarkers after sunitinib therapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Hematol Oncol. 2013 Jul 10;6(1):51. doi: 10.1186/1756-8722-6-51.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1756-8722-6-51](#)

AUTORES / AUTHORS: - Sahani DV; Jiang T; Hayano K; Duda DG; Catalano OA; Ancukiewicz M; Jain RK; Zhu AX

INSTITUCIÓN / INSTITUTION: - Division of Abdominal Imaging and Intervention, Harvard Medical School and Massachusetts General Hospital, 55 Fruit Street, White 270, Boston, MA 02114, USA. dsahani@partners.org.

RESUMEN / SUMMARY: - BACKGROUND: To investigate the hypothesis that MRI derived diffusion-weighted imaging (DWI) and perfusion (MRP) parameters are sensitive image biomarkers for monitoring early antiangiogenic effects and predicting progression free survival (PFS) in advanced hepatocellular carcinoma (HCC). METHODS: In this phase II clinical trial, 23 of 34 patients were included in the imaging and circulating biomarker study. DWI and MRP were performed at the baseline and at 2-weeks after initiation of sunitinib. The imaging protocol included an axial DWI sequence using b values of 50, 400 and 800 sec/mm², and MRP using a series of coronal 3D-VIBE following 20 ml of Gd-DTPA at 2 ml/sec. These parameters were compared with clinical outcome and PFS at 6-months. Correlation between changes in MRI parameters and plasma biomarkers was also evaluated. RESULTS: After 2-week of sunitinib, substantial K_{trans} changes in HCC were observed from median baseline value 2.15 min⁻¹ to 0.94 min⁻¹ (P = 0.0001) with increases in median apparent diffusion coefficient (ADC) from 0.88 x 10⁻³ mm²/s to 0.98 x 10⁻³ mm²/s (P = 0.0001). Tumor size remained unchanged by RECIST and mRECIST (both P > 0.05). Patients who showed larger drop in K_{trans} and Kep at 2 weeks correlated with favorable clinical outcome, and higher baseline K_{trans} and larger drop in EVF correlated with longer PFS (all P < 0.05). There was a significant association between a decrease in sVEGFR2 and the drop in K_{trans} and Kep (P = 0.044, P = 0.030), and a significant and borderline association between decrease in TNF-alpha and the drop in K_{trans} and Kep, respectively (P = 0.051, P = 0.035). CONCLUSION: In HCC, MRP may be a more sensitive biomarker in predicting early response and PFS following sunitinib than RECIST and mRECIST. TRIAL REGISTRATION: ClinicalTrials.gov: NCT00361309.

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----- [982]

TÍTULO / TITLE: - Undecylprodigiosin induced apoptosis in p388 cancer cells is associated with its binding to ribosome.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 14;8(6):e65381. doi: 10.1371/journal.pone.0065381. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0065381

AUTORES / AUTHORS: - Liu P; Wang YY; Qi X; Gu Q; Geng M; Li J

INSTITUCIÓN / INSTITUTION: - Key Laboratory of Marine Drugs, Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao, China ; Analysis and Testing Center, Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai, China.

RESUMEN / SUMMARY: - Prodigiosins (PGs) are a family of natural red pigments with anticancer activity, and one member of the family has entered clinical phase II trials. However, the anticancer mechanisms of PGs remain largely unclear. This study was designed to investigate the molecular basis of anticancer activity of UP, a derivative of PGs, in P388 cells. By introducing pharmacological inhibitors and utilizing a variety of analytical approaches including western blotting, flow cytometry and confocal laser microscopy, we found that UP inhibited proliferation of P388 via arresting cells at G2/M phase and inducing cells apoptosis, which was related to the activation of P38, JNK rather than ERK1/2 signaling. ROS regeneration and acidification in cells appear not involved in UP induced apoptosis. Furthermore, utilizing mass spectrometry, sucrose density gradient fractionation and immunofluorescence staining, we discovered that UP was apparently located at ribosome. These results together indicate that ribosome may be the potential target of UP in cancer cells, which opened a new avenue in delineating the anticancer mechanism of PGs.

[983]

TÍTULO / TITLE: - Ursolic acid simultaneously targets multiple signaling pathways to suppress proliferation and induce apoptosis in colon cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 May 30;8(5):e63872. doi: 10.1371/journal.pone.0063872. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0063872

AUTORES / AUTHORS: - Wang J; Liu L; Qiu H; Zhang X; Guo W; Chen W; Tian Y; Fu L; Shi D; Cheng J; Huang W; Deng W

INSTITUCIÓN / INSTITUTION: - State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Guangzhou, China.

RESUMEN / SUMMARY: - Ursolic acid (UA), a natural pentacyclic triterpenoid carboxylic acid distributed in medical herbs, exerts antitumor effects and is emerging as a promising compound for cancer prevention and therapy, but its excise mechanisms of action in colon cancer cells remains largely unknown. Here, we identified the molecular mechanisms by which UA inhibited cell proliferation and induced apoptosis in human colon cancer SW480 and LoVo cells. Treatment with UA led to significant inhibitions in cell viability and clone formation and changes in cell morphology and spreading. UA also suppressed colon cancer cell migration by inhibiting MMP9 and upregulating CDH1 expression. Further studies showed that UA inhibited the phosphorylation of Akt and ERK proteins. Pretreatment with an Akt or ERK-specific inhibitor considerably abrogated the proliferation inhibition by UA. UA also significantly inhibited colon cancer cell COX-2 expression and PGE2 production. Pretreatment with a COX-2 inhibitor (celecoxib) abrogated the UA-induced cell proliferation. Moreover, we found that UA effectively promoted NF-kappaB and p300 translocation from cell nuclei to cytoplasm, and attenuated the p300-mediated acetylation of NF-kappaB and CREB2. Pretreatment with a p300 inhibitor (roscovitine) abrogated the UA-induced cell proliferation, which is reversed by p300 overexpression. Furthermore, UA treatment induced colon cancer cell apoptosis, increased the cleavage of PARP, caspase-3 and 9, and triggered the release of cytochrome c from mitochondrial inter-membrane space into cytosol. These results indicate that UA inhibits cell proliferation and induces apoptosis in colon cancer cells through simultaneous modulation of the multiple signaling pathways such as MMP9/CDH1, Akt/ERK, COX-2/PGE2, p300/NF-kappaB/CREB2, and cytochrome c/caspase pathways.

[984]

TÍTULO / TITLE: - Apoptotic-like tumor cells and apoptotic neutrophils in mitochondrion-rich gastric adenocarcinomas: a comparative study with light and electron microscopy between these two forms of cell death.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Rare Tumors. 2013 Jun 7;5(2):68-71. doi: 10.4081/rt.2013.e18. Print 2013 Apr 15.

●● Enlace al texto completo (gratis o de pago) [4081/rt.2013.e18](#)

AUTORES / AUTHORS: - Caruso RA; Fedele F; Rigoli L; Branca G; Bonanno A; Quattrocchi E; Finocchiaro G; Venuti A

INSTITUCIÓN / INSTITUTION: - Department of Human Pathology and Department of Pediatrics, School of Medicine, University of Messina, Messina, Italy.

RESUMEN / SUMMARY: - ABSTRACT: Mitochondrion-rich adenocarcinomas represent a rare variant of gastric adenocarcinomas composed predominantly of columnar adenocarcinoma cells with eosinophilic cytoplasm, a strong supranuclear immunoreactivity for antimitochondrial antibody, and a marked neutrophil infiltration associated to tumor cell death. The purpose of this work is to investigate, using correlated light and electron microscopy, mitochondrion-

rich gastric adenocarcinomas focusing on the nature of the death in neoplastic cells and in infiltrating neutrophils. Adenocarcinoma cells, single or in small clusters, showed convoluted nuclei, irregularly condensed chromatin, loss of microvilli, and nuclear envelope dilatation. No nuclear fragmentation was observed in these dying cells and the plasma membrane did not show signs of disruption. These ultrastructural findings represent intermediate aspects between apoptosis and necrosis and are compatible with apoptosis-like programmed cell death. By contrast, some infiltrating neutrophils showed ultrastructural signs of classic apoptosis such as chromatin condensation into compact geometric (globular, crescent-shaped) figures, tightly packed cytoplasmic granules and intact cell membrane. Our study provides ultrastructural evidence of apoptosis-like tumour cell death in mitochondrion-rich gastric carcinomas and confirms that stereotyped outcome either as apoptosis or necrosis of tumor cells cannot always be expected in human neoplasms.

[985]

TÍTULO / TITLE: - Inclusion Complex of Zerumbone with Hydroxypropyl- beta - Cyclodextrin Induces Apoptosis in Liver Hepatocellular HepG2 Cells via Caspase 8/BID Cleavage Switch and Modulating Bcl2/Bax Ratio.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med.

2013;2013:810632. doi: 10.1155/2013/810632. Epub 2013 May 8.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/810632](#)

AUTORES / AUTHORS: - Muhammad Nadzri N; Abdul AB; Sukari MA; Abdelwahab SI; Eid EE; Mohan S; Kamalidehghan B; Anasamy T; Ng KB; Syam S; Arbab IA; Rahman HS; Ali HM

INSTITUCIÓN / INSTITUTION: - UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, University Putra Malaysia (UPM), Serdang, 43400 Selangor, Malaysia.

RESUMEN / SUMMARY: - Zerumbone (ZER) isolated from Zingiber zerumbet was previously encapsulated with hydroxypropyl- beta -cyclodextrin (HP beta CD) to enhance ZER's solubility in water, thus making it highly tolerable in the human body. The anticancer effects of this new ZER-HP beta CD inclusion complex via apoptosis cell death were assessed in this study for the first time in liver hepatocellular cells, HepG2. Apoptosis was ascertained by morphological study, nuclear stain, and sub-G1 cell population accumulation with G2/M arrest. Further investigations showed the release of cytochrome c and loss of mitochondrial membrane potential, proving mitochondrial dysfunction upon the ZER-HP beta CD treatment as well as modulating proapoptotic and anti-apoptotic Bcl-2 family members. A significant increase in caspase 3/7, caspase 9, and caspase 8 was detected with the depletion of BID cleaved by caspase 8. Collectively, these results prove that a highly soluble inclusion complex of ZER-HP beta CD could be a promising anticancer agent for the treatment of hepatocellular carcinoma in humans.

[986]

TÍTULO / TITLE: - Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Asian Pac J Cancer Prev. 2013;14(4):2311-5.

AUTORES / AUTHORS: - Zhang Q; Geng PL; Yin P; Wang XL; Jia JP; Yao J

INSTITUCIÓN / INSTITUTION: - Department of Orthopedics, Chinese PLA General Hospital, Beijing, China.

RESUMEN / SUMMARY: - **OBJECTIVE:** To investigate the expression level of TUG1 and one of its transcript variants (n377360) in osteosarcoma cells and assess the role of TUG1 in proliferation and apoptosis in the U2OS cell line. **METHODS:** TUG1 and n377360 expression levels in patients with osteosarcomas and the U2OS human osteosarcoma cell line were evaluated using real-time quantitative PCR. U2OS cells were transfected with TUG1 and n377360 siRNA or non-targeting siRNA. MTS was performed to assess the cell proliferation and flow cytometry was applied to analyze apoptosis. **RESULTS:** We found significantly higher TUG1 and n377360 expression levels in osteosarcoma tissues compared with matched non-tumorous tissues. In line with this, suppression of TUG1 and n377360 expression by siRNA significantly impaired the cell proliferation potential of osteosarcoma cells. Furthermore, inhibition of TUG1 expression significantly promoted osteosarcoma cell apoptosis. **CONCLUSIONS:** The overexpression of TUG1 and n377360 in osteosarcoma specimens and the functional role of TUG1 and n377360 regarding cell proliferation and apoptosis in an osteosarcoma cell line provided evidence that the use of TUG1 or n377360 may be a viable but as yet unexplored therapeutic strategy in tumors that over express these factors.

[987]

TÍTULO / TITLE: - Anticancer activity of Saussurea lappa extract by apoptotic pathway in KB human oral cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Pharm Biol. 2013 Jul 16.

●● [Enlace al texto completo \(gratis o de pago\)](#)

[3109/13880209.2013.792847](#)

AUTORES / AUTHORS: - Moon SM; Yun SJ; Kook JK; Kim HJ; Choi MS; Park BR; Kim SG; Kim BO; Lee SY; Ahn H; Chun HS; Kim DK; Kim CS

INSTITUCIÓN / INSTITUTION: - Oral Biology Research Institute, Chosun University, Dong-Gu, Gwangju, Republic of Korea.

RESUMEN / SUMMARY: - Abstract Context: Saussurea lappa Dence (Compositae) is used as a traditional herbal medicine to treat abdominal pain and tenesmus in East Asia. Current studies have shown that S. lappa has anticancer activity in divergent of cancer cells. However, the effects of S. lappa

on oral cancer and its mechanisms of action have yet to be elucidated. Objective: To explore its potential chemotherapeutic effects and mechanism of cell growth inhibition on human oral cancer cells. Materials and methods: The dried roots of *S. lappa* were used in this study. Cell viability of KB cells was evaluated by 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide assay after treatment with 30 microg/ml of methanol extract from the dried roots of *S. lappa*. To understand whether its effect on cell death is related with apoptosis pathway, we performed DNA fragmentation assay, western blot, caspase activity assay and fluorescence-activated cell sorting (FACS) analysis. Results: Treatment of *S. lappa* extract onto KB cells reduced cell viability significantly with an IC50 value of 30 microg/ml. The formation of a DNA ladder was observed starting at the 24 h treatment. In western blotting analysis, the *S. lappa* extract induced the proteolytic processing of caspase-3, -9 and poly (ADP-ribose) polymerase, a significant increase of Bax and marked reduction of Bcl-2. We also confirmed the activation of caspase-3/-7 in living KB cells by fluorescence microscopy. Conclusion: These results suggested that *S. lappa* extract inhibited cell proliferation through the apoptosis pathway in KB human oral cancer cells.

[988]

TÍTULO / TITLE: - Apoptotic effect of hot water extract of *L.* in human oral cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Oncol Lett. 2012 Sep;4(3):489-494. Epub 2012 Jun 8.

●● Enlace al texto completo (gratis o de pago) [3892/ol.2012.748](#)

AUTORES / AUTHORS: - Shin JA; Kim JS; Kwon KH; Nam JS; Jung JY; Cho NP; Cho SD

INSTITUCIÓN / INSTITUTION: - Department of Oral Pathology, School of Dentistry, Institute of Oral Bioscience, Chonbuk National University, Jeonju.

RESUMEN / SUMMARY: - *Sanguisorba officinalis* L. has been used in traditional Asian medicine to treat diseases including diarrhea, chronic intestinal infections, duodenal ulcers and bleeding. This study examined the antiproliferative effects and apoptotic activity of hot water extract of *S. officinalis* L. (HESO) on HSC4 and HN22 human oral cancer cells. The effects of HESO were evaluated by the 3-(4,5-dimethylthiazol-2-yl)-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium (MTS) assay, 4',6-diamidino-2-phenylindole (DAPI) staining and western blot analysis. HESO was found to inhibit cell growth and induce apoptosis in HSC4 and HN22 oral cancer cells. HESO downregulated myeloid cell leukemia-1 (Mcl-1) in HSC4 cells and was associated with the activation of Bak, resulting in Bak oligomerization on the mitochondrial outer membrane. HESO did not alter Mcl-1 expression in HN22 cells, but it decreased Sp1 expression. The downregulation of Sp1 by HESO in HN22 cells resulted in a decrease in survivin, a downstream target protein of Sp1. These results suggested that HESO inhibited the growth of oral cancer through either Mcl-1 or

Sp1, indicating that HESO may serve as a potential drug candidate against oral cancer.

[989]

TÍTULO / TITLE: - Involvement of Nrf2-mediated upregulation of heme oxygenase-1 in mollugin-induced growth inhibition and apoptosis in human oral cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Biomed Res Int. 2013;2013:210604. doi: 10.1155/2013/210604. Epub 2013 May 2.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/210604](#)

AUTORES / AUTHORS: - Lee YM; Auh QS; Lee DW; Kim JY; Jung HJ; Lee SH; Kim EC

INSTITUCIÓN / INSTITUTION: - Department of Maxillofacial Tissue Regeneration and Research Center for Tooth & Periodontal Regeneration, School of Dentistry, Kyung Hee University, 1 Heogi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.

RESUMEN / SUMMARY: - Although previous studies have shown that mollugin, a bioactive phytochemical isolated from *Rubia cordifolia* L. (Rubiaceae), exhibits antitumor effects, its biological activity in oral cancer has not been reported. We thus investigated the effects and putative mechanism of apoptosis induced by mollugin in human oral squamous cell carcinoma cells (OSCCs). Results show that mollugin induces cell death in a dose-dependent manner in primary and metastatic OSCCs. Mollugin-induced cell death involved apoptosis, characterized by the appearance of nuclear shrinkage, flow cytometric analysis of sub-G1 phase arrest, and annexin V-FITC and propidium iodide staining. Western blot analysis and RT-PCR revealed that mollugin suppressed activation of NF- κ B and NF- κ B-dependent gene products involved in antiapoptosis (Bcl-2 and Bcl-xl), invasion (MMP-9 and ICAM-1), and angiogenesis (FGF-2 and VEGF). Furthermore, mollugin induced the activation of p38, ERK, and JNK and the expression of heme oxygenase-1 (HO-1) and nuclear factor E2-related factor 2 (Nrf2). Mollugin-induced growth inhibition and apoptosis of HO-1 were reversed by an HO-1 inhibitor and Nrf2 siRNA. Collectively, this is the first report to demonstrate the effectiveness of mollugin as a candidate for a chemotherapeutic agent in OSCCs via the upregulation of the HO-1 and Nrf2 pathways and the downregulation of NF- κ B.

[990]

TÍTULO / TITLE: - Photodynamic therapy with talaporfin sodium induces dose-dependent apoptotic cell death in human glioma cell lines.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Photodiagnosis Photodyn Ther. 2013 May;10(2):103-10. doi: 10.1016/j.pdpdt.2012.08.002. Epub 2012 Sep 25.

- Enlace al texto completo (gratis o de pago)

1016/j.pdpdt.2012.08.002

AUTORES / AUTHORS: - Tsutsumi M; Miki Y; Akimoto J; Haraoka J; Aizawa K; Hirano K; Beppu M

INSTITUCIÓN / INSTITUTION: - Department of Neurosurgery, Tokyo Medical University, Japan.

RESUMEN / SUMMARY: - **OBJECTIVE:** To investigate the kinetics of cell death in human glioma cell lines induced by photodynamic therapy (PDT) with the second-generation photosensitizer talaporfin sodium (TS) and a 664-nm diode laser. **MATERIALS AND METHODS:** Three human glioma cell lines (T98G, A172, U251) were studied. After incubation of the cell lines with various concentrations of TS for 4 h, PDT using diode laser irradiation at 33 mW/cm² and 10 J/cm² was performed. Cell viability and changes in cell morphology were examined by the Cell Counting Kit-8 assay and phase-contrast microscopy, respectively. In addition, to evaluate the pathology of cell death, changes in cell viability after treatment with a caspase activation inhibitor and an autophagy inhibitor were also examined. **RESULTS:** In all 3 human glioma cell lines, TS induced dose-dependent cell death. However, the 50% lethal dose of TS varied among these cell lines. The main morphological feature of cell death was shrinkage of the cell body, and the number of cells with this morphological change increased in a time-dependent manner, resulting in cell death. In addition, a dose-dependent improvement in cell viability by the caspase inhibitor Z-VAD-fmk was observed. **CONCLUSION:** PDT with TS induces dose-dependent apoptosis in human glioma cell lines. However, the sensitivity to PDT varied among the cell lines, indicating a possible difference in the intracellular content of TS, or a difference in the susceptibility to the intracellular oxidative stress caused by PDT.

[991]

TÍTULO / TITLE: - Quantitative expression analysis and prognostic significance of the BCL2-associated X gene in nasopharyngeal carcinoma: a retrospective cohort study.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 Jun 18;13:293. doi: 10.1186/1471-2407-13-293.

- Enlace al texto completo (gratis o de pago) 1186/1471-2407-13-293

AUTORES / AUTHORS: - Kontos CK; Fendri A; Khabir A; Mokdad-Gargouri R; Scorilas A

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, University of Athens, Panepistimiopolis, Athens, 15701, Greece.

ascorilas@biol.uoa.gr.

RESUMEN / SUMMARY: - **BACKGROUND:** Nasopharyngeal carcinoma (NPC) is a highly metastatic epithelial malignancy showing high prevalence in Southeast Asia and North Africa. The BCL2-associated X (BAX) gene encodes the most

important pro-apoptotic member of the BCL2 family. We have recently shown that BCL2 and BCL2L12, two other members of the same apoptosis-related family, possess significant prognostic value in NPC. The objective of the current study was to analyze BAX mRNA expression in nasopharyngeal biopsies of NPC patients, and to assess its prognostic potential in this disease. **METHODS:** Total RNA was isolated from 88 malignant and 9 hyperplastic nasopharyngeal biopsies, resected from Tunisian patients. After cDNA synthesis by reverse transcription of polyadenylated RNA, BAX mRNA expression was analyzed using a highly sensitive quantitative real-time polymerase chain reaction (qRT-PCR) method. **RESULTS:** Lower BAX mRNA levels were detected in NPC biopsies than in hyperplastic nasopharyngeal samples. BAX mRNA expression status was associated with low tumor extent, negative regional lymph node status, and absence of distant metastases. Kaplan-Meier survival analysis demonstrated that patients with BAX mRNA-positive NPC have significantly longer disease-free survival (DFS) and overall survival (OS). In accordance with these findings, Cox regression analysis revealed that BAX mRNA expression can be considered as a favorable prognostic indicator of DFS and OS in NPC, independent of their gender, age, tumor histology, tumor extent, and nodal status. Furthermore, NPC patients without distant metastases are less likely to relapse when their primary tumor is BAX mRNA-positive, compared to metastasis-free patients with a BAX-negative nasopharyngeal malignancy. **CONCLUSION:** This is the first study examining the potential clinical utility of BAX as a prognostic tumor biomarker in NPC. We provide evidence that BAX mRNA expression can be considered as an independent favorable prognostic indicator of DFS and OS in NPC.

[992]

TÍTULO / TITLE: - Prognostic significance of C-reactive protein polymorphism and KRAS/BRAF in synchronous liver metastasis from colorectal cancer.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - PLoS One. 2013 Jun 3;8(6):e65117. doi: 10.1371/journal.pone.0065117. Print 2013.

●● Enlace al texto completo (gratis o de pago)

1371/journal.pone.0065117

AUTORES / AUTHORS: - Huang CJ; Teng HW; Chien CC; Lin JK; Yang SH

INSTITUCIÓN / INSTITUTION: - Department of Medical Research, Cathay General Hospital, Taipei, Taiwan.

RESUMEN / SUMMARY: - **BACKGROUND:** The liver is the most common target organ in the metastasis of colorectal cancer (CRC). Synchronous liver metastases may confer a poorer prognosis than metachronous metastases, and genetic alterations and an inflammatory response have also been associated with a poor prognosis in cases of a liver metastasis arising from CRC. However, few studies have examined the relationship between KRAS mutations and inflammatory status in CRC, especially with respect to liver metastases.

METHODS: The effect of the activated mitogen-activated protein kinase pathway and another protein involved in inflammation, C-reactive protein, in liver metastases were examined. We aimed to determine the impact of the CRP-specific single nucleotide polymorphism (SNP) rs7553007 in liver metastasis on the CRC-specific survival (CSS) of patients after colorectal liver metastasectomy. **RESULTS:** We found no significant differences in genotype distributions and allele frequencies at the CRP SNP rs7553007 between CRC patients with liver metastasis and the control group. CSS rates were low in the subgroup of patients with synchronous metastasis with the A-allele (A/A and A/G) at rs7553007 or mutated KRAS/BRAF in liver metastatic specimens. Furthermore, the CRP SNP rs7553007 (hazard ratio [HR] = 1.101; 95% confidence interval [CI] = 1.011-1.200; P = 0.027) and KRAS/BRAF mutations (HR = 2.377; 95% CI = 1.293-4.368; P = 0.005) remained predictive for the CSS of CRC patients with synchronous liver metastasis in multivariate analysis. **CONCLUSIONS:** Both the CRP SNP rs7553007 and KRAS/BRAF mutations were independent prognostic factors for CRC patients with synchronous liver metastasis.

[993]

TÍTULO / TITLE: - Molecular mechanisms of action and potential biomarkers of growth inhibition of dasatinib (BMS-354825) on hepatocellular carcinoma cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Cancer. 2013 May 30;13(1):267.

●● Enlace al texto completo (gratis o de pago) [1186/1471-2407-13-267](#)

AUTORES / AUTHORS: - Chang AY; Wang M

RESUMEN / SUMMARY: - **BACKGROUND:** Molecular targeted therapy has emerged as a promising treatment of Hepatocellular carcinoma (HCC). One potential target is the Src family Kinase (SFK). C-Src, a non-receptor tyrosine kinase is a critical link of multiple signal pathways that regulate proliferation, invasion, survival, metastasis, and angiogenesis. In this study, we evaluated the effects of a novel SFK inhibitor, dasatinib (BMS-354825), on SFK/FAK/p130CAS, PI3K/PTEN/Akt/mTOR, Ras/Raf/MAPK and Stats pathways in 9 HCC cell lines. **METHODS:** Growth inhibition was assessed by MTS assay. EGFR, Src and downstream proteins FAK, Akt, MAPK42/44, Stat3 expressions were measured by western blot. Cell adhesion, migration and invasion were performed with and without dasatinib treatment. **RESULTS:** The IC50 of 9 cell lines ranged from 0.7 μM ~ 14.2 μM. In general the growth inhibition by dasatinib was related to total Src (t-Src) and the ratio of activated Src (p-Src) to t-Src. There was good correlation of the sensitivity to dasatinib and the inhibition level of p-Src, p-FAK576/577 and p-Akt. No inhibition was found on Stat3 and MAPK42/44 in all cell lines. The inhibition of cell adhesion, migration and invasion were correlated with p-FAK inhibition. **CONCLUSION:** Dasatinib inhibits the proliferation, adhesion, migration and invasion of HCC cells in vitro via inhibiting of Src tyrosine kinase and affecting SFK/FAK and

PI3K/PTEN/Akt, but not Ras/Raf/MEK/ERK and JAK/Stat pathways. T-Src and p-Src/t-Src may be useful biomarkers to select HCC patients for dasatinib treatment.

[994]

TÍTULO / TITLE: - A novel system enhancing the endosomal escapes of peptides promotes Bak BH3 peptide inducing apoptosis in lung cancer A549 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Target Oncol. 2013 Jun 6.

●● Enlace al texto completo (gratis o de pago) [1007/s11523-013-0282-](#)

[9](#)

AUTORES / AUTHORS: - Lin N; Zheng W; Li L; Liu H; Wang T; Wang P; Ma X

INSTITUCIÓN / INSTITUTION: - School of Biotechnology and State Key Laboratory of Bioreactor Engineering, East China University of Science and Technology, Shanghai, 200237, China.

RESUMEN / SUMMARY: - Therapeutic peptides have been proven useful for treating various diseases. However, it is difficult for therapeutic peptides to reach their target sites with an effective concentration due to inefficient intracellular delivery. Although Tat transduction peptide is a promising tool to deliver therapeutic peptides into cells, the entrapment within endosomes and the nuclear localization of Tat transduction peptide severely limited the biological effects of Tat-linked cargos. In this study, we designed a novel peptide delivering system, Tat-INF7-ubiquitin (TIU), which consisted of Tat transduction peptide, endosomal escape enhancer peptide INF7, and ubiquitin protein. We found that the TIU system was able to efficiently deliver the mCherry fluorescent proteins and the apoptosis-inducing Bak BH3 peptide into the cytosol. The Bak BH3 peptide transported into the cells by the TIU system increased the apoptotic rate to 46.15 +/- 4.86 % (p < 0.001) in A549 cells, while Tat-BH3 could result in only 20.45 +/- 2.89 %. These results demonstrated that the TIU system could enhance the effects of therapeutic peptides by facilitating the transmembrane delivery of peptides into the cells and the escape of target proteins from the endosome efficiently.

[995]

TÍTULO / TITLE: - Pathological predictive factors for tumor response in locally advanced breast carcinomas treated with anthracyclin-based neoadjuvant chemotherapy.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - J Cancer Res Ther. 2013 Apr-Jun;9(2):245-9. doi: 10.4103/0973-1482.113366.

●● Enlace al texto completo (gratis o de pago) [4103/0973-](#)

[1482.113366](#)

AUTORES / AUTHORS: - Patel T; Gupta A; Shah M

INSTITUCIÓN / INSTITUTION: - Department of Pathology, Gujarat Cancer and Research Institute, M.P Shah Cancer Hospital, Ahmedabad, Gujarat, India.

RESUMEN / SUMMARY: - AIM: Neoadjuvant chemotherapy (NACT) is used as a primary treatment for locally advanced breast carcinoma (LABC) and also extended to operable breast cancer. The aim of this study was to evaluate the predictive value of different histological parameters in core biopsy of LABC patients treated with anthracycline-based chemotherapy regimen. Pathological assessment of the excised tumor bed is the gold standard and is essential for identifying the group of patients with pathologic complete response (pCR) or pathologic noncomplete response (pNR). MATERIALS AND METHODS: A total of 50 patients with stage II and III breast carcinoma were included in the study. Pretreatment core biopsy histological features include tumor type, histological grade, presence of tumor necrosis, lymphovascular emboli (LVE) and immunohistochemical stains for estrogen receptor (ER) and progesterone receptor (PR) were obtained. Patients were given 3-6 cycles of NACT. Pathological response was assessed. RESULT: Seven out of 50 patients achieved pCR. A total of 71.4% patients who achieved pCR had tumor necrosis on initial core biopsy while only 30% pNR cases had this feature (P =0.035). Breast carcinoma other than ductal type was chemoresistant. Of 47 core biopsies, LVE was observed in 13 cases (28 %) of which 11 showed axillary node metastasis. None of these 13 cases had pCR, thus having poor predictive value. CONCLUSION: Pathological parameters like type of tumor, presence of LVE and tumor necrosis in the core biopsy can predict the response to NACT in routine stain. Tumor necrosis and type of breast carcinoma are predictive parameters for tumor responsiveness to NACT. LVE was reliable in predicting axillary lymph node metastasis.

[996]

TÍTULO / TITLE: - Anthricin Isolated from *Anthriscus sylvestris* (L.) Hoffm. Inhibits the Growth of Breast Cancer Cells by Inhibiting Akt/mTOR Signaling, and Its Apoptotic Effects Are Enhanced by Autophagy Inhibition.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:385219. doi: 10.1155/2013/385219. Epub 2013 May 29.

●● Enlace al texto completo (gratis o de pago) [1155/2013/385219](#)

AUTORES / AUTHORS: - Jung CH; Kim H; Ahn J; Jung SK; Um MY; Son KH; Kim TW; Ha TY

INSTITUCIÓN / INSTITUTION: - Department of Food Biotechnology, University of Science and Technology, Daejeon 305-806, Republic of Korea ; Division of Metabolism and Functionality Research, Korea Food Research Institute, 1201 Anyangpangyo-ro, Seongnam 463-746, Republic of Korea.

RESUMEN / SUMMARY: - Anthricin (deoxypodophyllotoxin) is a natural product isolated from *Anthriscus sylvestris* (L.) Hoffm. (Apiaceae). Here, we investigated the effect of anthricin on autophagy and mammalian target of rapamycin

(mTOR) signaling as anticancer actions in breast cancer cells. Many studies have supported the contention that the phosphoinositide 3-kinase (PI3K)/Akt/mTORC1 pathway is considerably deregulated in breast cancer and that autophagy plays important roles in the development of this type of cancer, although the exact underlying mechanisms remain unknown. Our data confirmed that anthriscin markedly induced apoptosis in 2 breast cancer cell lines, MCF7 (estrogen receptor positive) and MDA-MB-231 (estrogen receptor, progesterone receptor, and Her2/Neu receptor negative). Anthriscin treatment decreased the levels of phosphorylated Akt and mTORC1, followed by inhibition of cell growth. Interestingly, blockage of autophagy by a pharmacological inhibitor or genetic deletion of ULK1 and Atg13 accelerated anthriscin-induced apoptosis, suggesting that autophagy has cytoprotective effects. Taken together, our results indicate that anthriscin is an inhibitor of mTOR and that a combination of an autophagy inhibitor and anthriscin may serve as a new promising strategy for the treatment of breast cancer cells.

[997]

TÍTULO / TITLE: - Wentilactone B induces G2/M phase arrest and apoptosis via the Ras/Raf/MAPK signaling pathway in human hepatoma SMMC-7721 cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Cell Death Dis. 2013 Jun 6;4:e657. doi: 10.1038/cddis.2013.182.

●● Enlace al texto completo (gratis o de pago) [1038/cddis.2013.182](#)

AUTORES / AUTHORS: - Zhang Z; Miao L; Lv C; Sun H; Wei S; Wang B; Huang C; Jiao B

INSTITUCIÓN / INSTITUTION: - Department of Biochemistry and Molecular Biology, Faculty of Basic Medicine, Second Military Medical University, Shanghai, China.

RESUMEN / SUMMARY: - Hepatocellular carcinoma (HCC) is generally acknowledged as the most common primary malignant tumor, and it is known to be resistant to conventional chemotherapy. Wentilactone B (WB), a tetranorditerpenoid derivative extracted from the marine algae-derived endophytic fungus *Aspergillus wentii* EN-48, has been shown to trigger apoptosis and inhibit metastasis in HCC cell lines. However, the mechanisms of its antitumor activity remain to be elucidated. We report here that WB could significantly induce cell cycle arrest at G2 phase and mitochondrial-related apoptosis, accompanying the accumulation of reactive oxygen species (ROS). Additionally, treatment with WB induced phosphorylation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), but not p38 MAP kinase. Among the pathway inhibitors examined, only SP600125 (JNK inhibitor) markedly reversed WB-induced apoptosis, and only U0126 (ERK inhibitor) significantly blocked WB-triggered G2 phase arrest. We also found that WB treatment increased both Ras and Raf activation, and transfection of cells with dominant-negative Ras (RasN17) abolished WB-induced apoptosis and G2 phase arrest in SMMC-7721 cells. Furthermore, the results of inverse docking

(INVDock) analysis suggested that WB could bind to Ras-GTP, and the direct binding affinity was also confirmed by surface plasmon resonance (SPR). Finally, in vivo, WB suppressed tumor growth in mouse xenograft models. Taken together, these results indicate that WB induced G2/M phase arrest and apoptosis in human hepatoma SMMC-7721 cells via the Ras/Raf/ERK and Ras/Raf/JNK signaling pathways, and this agent may be a potentially useful compound for developing anticancer agents for HCC.

[998]

TÍTULO / TITLE: - Induction of apoptosis in melanoma A375 cells by a chloroform fraction of *Centratherum anthelminticum* (L.) seeds involves NF-kappaB, p53 and Bcl-2-controlled mitochondrial signaling pathways.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - BMC Complement Altern Med. 2013 Jul 10;13:166. doi: 10.1186/1472-6882-13-166.

●● [Enlace al texto completo \(gratis o de pago\) 1186/1472-6882-13-166](#)

AUTORES / AUTHORS: - Looi CY; Moharram B; Paydar M; Wong YL; Leong KH; Mohamad K; Arya A; Wong WF; Mustafa MR

INSTITUCIÓN / INSTITUTION: - Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. looicy@um.edu.my

RESUMEN / SUMMARY: - BACKGROUND: *Centratherum anthelminticum* (L.) Kuntze (scientific synonyms: *Vernonia anthelmintica*; black cummin) is one of the ingredients of an Ayurvedic preparation, called “Kayakalp”, commonly applied to treat skin disorders in India and Southeast Asia. Despite its well known anti-inflammatory property on skin diseases, the anti-cancer effect of *C. anthelminticum* seeds on skin cancer is less documented. The present study aims to investigate the anti-cancer effect of *Centratherum anthelminticum* (L.) seeds chloroform fraction (CACF) on human melanoma cells and to elucidate the molecular mechanism involved. METHODS: A chloroform fraction was extracted from *C. anthelminticum* (CACF). Bioactive compounds of the CACF were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Human melanoma cell line A375 was treated with CACF in vitro. Effects of CACF on growth inhibition, morphology, stress and survival of the cell were examined with MTT, high content screening (HSC) array scan and flow cytometry analyses. Involvement of intrinsic or extrinsic pathways in the CACF-induced A375 cell death mechanism was examined using a caspase luminescence assay. The results were further verified with different caspase inhibitors. In addition, Western blot analysis was performed to elucidate the changes in apoptosis-associated molecules. Finally, the effect of CACF on the NF-kappaB nuclear translocation ability was assayed. RESULTS: The MTT assay showed that CACF dose-dependently inhibited cell growth of A375, while exerted less cytotoxic effect on normal primary epithelial melanocytes. We demonstrated that CACF induced cell growth inhibition through apoptosis, as evidenced by cell shrinkage, increased annexin V staining and formation of

membrane blebs. CACF treatment also resulted in higher reactive oxygen species (ROS) production and lower Bcl-2 expression, leading to decrease mitochondrial membrane potential (MMP). Disruption of the MMP facilitated the release of mitochondrial cytochrome c, which activates caspase-9 and downstream caspase-3/7, resulting in DNA fragmentation and up-regulation of p53 in melanoma cells. Moreover, CACF prevented TNF-alpha-induced NF-kappaB nuclear translocation, which further committed A375 cells toward apoptosis. CONCLUSIONS: Together, our findings suggest CACF as a potential therapeutic agent against human melanoma malignancy.

[999]

TÍTULO / TITLE: - The mechanisms of chansu in inducing efficient apoptosis in colon cancer cells.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Evid Based Complement Alternat Med. 2013;2013:849054. doi: 10.1155/2013/849054. Epub 2013 May 30.

●● [Enlace al texto completo \(gratis o de pago\) 1155/2013/849054](#)

AUTORES / AUTHORS: - Li C; Hashimi SM; Cao S; Mellick AS; Duan W; Good D; Wei MQ

INSTITUCIÓN / INSTITUTION: - Division of Molecular and Gene Therapies, Griffith Health Institute and School of Medical Science, Griffith University, Gold Coast, QLD 4222, Australia.

RESUMEN / SUMMARY: - Chansu is one of the most widely used traditional Chinese medicines in China, Japan, and other Southeast Asian countries primarily for antipain, anti-inflammation, and recently anticancer. Over 10 recipes and remedies contained Chansu, which are easily available in pharmacies and hospitals, but the mechanisms of action were not clearly articulated. In the present study, Cinobufagin (CBF), the major compound of Chansu, was employed as a surrogate marker to determine its ability in inducing cancer cell death. As expected, CBF has significant cancer-killing capacity for a range of cancers, but such ability differs markedly. Colon and prostate cancers are more sensitive than skin and lung cancers. Interestingly, cancer cells die through apoptotic pathway either being biphasic caspase-3-dependent (HCT116) or independent (HT29). Multipathway analysis reveals that CBF-induced apoptosis is likely modulated by the hypoxia-inducing factor-1 alpha subunit (HIF-1 alpha) as its inhibition was evident in vitro and in vivo. Taken together, these results demonstrate that CBF is a potent apoptotic inducer with potential for further development as a novel and effective anticancer agent for a range of cancers, especially colon cancer.

[1000]

TÍTULO / TITLE: - Genome evolution predicts genetic interactions in protein complexes and reveals cancer drug targets.

RESUMEN / SUMMARY: - [Enlace al Resumen / Link to its Summary](#)

REVISTA / JOURNAL: - Nat Commun. 2013 Jul 11;4:2124. doi:
10.1038/ncomms3124.

●● Enlace al texto completo (gratis o de pago) [1038/ncomms3124](https://doi.org/10.1038/ncomms3124)

AUTORES / AUTHORS: - Lu X; Kensche PR; Huynen MA; Notebaart RA

INSTITUCIÓN / INSTITUTION: - Department of Bioinformatics (CMBI), Centre for
Molecular Life Sciences, Radboud University Medical Centre, 6525GA
Nijmegen, The Netherlands.

RESUMEN / SUMMARY: - Genetic interactions reveal insights into cellular function and can be used to identify drug targets. Here we construct a new model to predict negative genetic interactions in protein complexes by exploiting the evolutionary history of genes in parallel converging pathways in metabolism. We evaluate our model with protein complexes of *Saccharomyces cerevisiae* and show that the predicted protein pairs more frequently have a negative genetic interaction than random proteins from the same complex. Furthermore, we apply our model to human protein complexes to predict novel cancer drug targets, and identify 20 candidate targets with empirical support and 10 novel targets amenable to further experimental validation. Our study illustrates that negative genetic interactions can be predicted by systematically exploring genome evolution, and that this is useful to identify novel anti-cancer drug targets.
