

BREAKING ADVANCES

- 7345 | **Highlights from Recent Cancer Literature**

REVIEWS

- 7347 | **CRLF2 and JAK2 in B-Progenitor Acute Lymphoblastic Leukemia: A Novel Association in Oncogenesis**
J. Devon Roll and Gary W. Reuther
- 7353 | **PALB2/FANCN: Recombining Cancer and Fanconi Anemia**
Marc Tischkowitz and Bing Xia

MEETING REPORTS

- 7360 | **AACR Special Conference on Epithelial-Mesenchymal Transition and Cancer Progression and Treatment**
Evanthia T. Roussos, Zuzana Keckesova, John D. Haley, David M. Epstein, Robert A. Weinberg, and John S. Condeelis
- 7365 | **The Role of Telomeres and Telomerase in Cancer Research**
Sheila A. Stewart and Alison A. Bertuch
- 7372 | **Thirteenth AACR Special Conference on Cancer Epigenetics**
Jason P. Ross and Peter L. Molloy

CLINICAL STUDIES

- 7379 | **MLH1 Founder Mutations with Moderate Penetrance in Spanish Lynch Syndrome Families**
Ester Borràs, Marta Pineda, Ignacio Blanco, Ethan M. Jewett, Fei Wang, Àlex Teulé, Trinidad Caldés, Miguel Urioste, Cristina Martínez-Bouzas, Joan Brunet, Judith Balmaña, Asunción Torres, Teresa Ramón y Cajal, Judit Sanz, Lucía Pérez-Cabornero, Sergi Castellví-Bel, Ángel Alonso, Ángel Lanas, Sara González, Víctor Moreno, Stephen B. Gruber, Noah A. Rosenberg, Bhramar Mukherjee, Conxi Lázaro, and Gabriel Capellá
- Précis: Findings on founder mutations in Lynch syndrome have implications for molecular diagnosis and genetic counseling.*

- 7392 | **Clinical Pharmacology of Resveratrol and Its Metabolites in Colorectal Cancer Patients**

Ketan R. Patel, Victoria A. Brown, Donald J.L. Jones, Robert G. Britton, David Hemingway, Andrew S. Miller, Kevin P. West, Tristan D. Booth, Marjorie Perloff, James A. Crowell, Dean E. Brenner, William P. Steward, Andreas J. Gescher, and Karen Brown

Précis: Study argues that clinically safe and pharmacologically relevant doses of the red wine compound resveratrol can be achieved in colorectal patients for chemoprevention testing.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 7400 | **Hyperpolarized ¹³C Spectroscopic Imaging Informs on Hypoxia-Inducible Factor-1 and Myc Activity Downstream of Platelet-Derived Growth Factor Receptor**
Hagit Dafni, Peder E.Z. Larson, Simon Hu, Hikari A.I. Yoshihara, Christopher S. Ward, Humsa S. Venkatesh, Chunsheng Wang, Xiaoliang Zhang, Daniel B. Vigneron, and Sabrina M. Ronen

Précis: Results identify a noninvasive imaging strategy that offers the ability to detect the molecular pharmacodynamic effects of various cell signaling inhibitors, an important need in clinical development of targeted oncologic drugs.

MICROENVIRONMENT AND IMMUNOLOGY

- 7411 | **Activation-Induced Cytidine Deaminase Accelerates Clonal Evolution in BCR-ABL1-Driven B-Cell Lineage Acute Lymphoblastic Leukemia**
Tanja Andrea Gruber, Mi Sook Chang, Richard Sposto, and Markus Müschen

Précis: A B-cell process required for somatic hypermutation and immunoglobulin class switching can contribute to drug resistance in BCR-ABL1-driven acute lymphoblastic leukemias.

7421 **ERBB Receptor Activation Is Required for Profibrotic Responses to Transforming Growth Factor β**

Mahefatiana Andrianifahanana, Mark C. Wilkes, Claire E. Repellin, Maryanne Edens, Theodore J. Kottom, Rod A. Rahimi, and Edward B. Leof

Précis: Findings suggest a rationale to clinically evaluate EGF antagonists in tumors where receptor amplification is not observed, based on critical roles for EGF family signaling in tumor stromal cells.

7431 **Antibody-Dependent Natural Killer Cell-Mediated Cytotoxicity Engendered by a Kinase-Inactive Human HER2 Adenovirus-Based Vaccination Mediates Resistance to Breast Tumors**

Chiara Triulzi, Simona Vertuani, Claudia Curcio, Agnese Antognoli, Josef Seibt, Göran Akusjärvi, Wei-Zen Wei, Federica Cavallo, and Rolf Kiessling

Précis: Findings establish a critical role for natural killer cell activity in triggering antibody-dependent killing of HER2-expressing tumor cells, suggesting that promoting this activity may augment the efficacy of cancer vaccines which elicit antibody responses.

7442 **Amplifying TLR-MyD88 Signals within Tumor-Specific T Cells Enhances Antitumor Activity to Suboptimal Levels of Weakly Immunogenic Tumor Antigens**

Degui Geng, Liqin Zheng, Ratika Srivastava, Cruz Velasco-Gonzalez, Adam Riker, Svetomir N. Markovic, and Eduardo Davila

Précis: Activating TLR-MyD88 signals within tumor-specific T cells enhances the antitumor activity to suboptimal levels of subdominant tumor antigens.

7455 **Targeting Stat3 in the Myeloid Compartment Drastically Improves the *In vivo* Antitumor Functions of Adoptively Transferred T Cells**

Andreas Herrmann, Marcin Kortylewski, Maciej Kujawski, Chunyan Zhang, Karen Reckamp, Brian Armstrong, Lin Wang, Claudia Kowolik, Jiehui Deng, Robert Figlin, and Hua Yu

Précis: Results suggest strategies to reduce ex vivo manipulation and overcome tumor-induced immunosuppression of adoptive T-cell therapies, representing two major challenges in the field.

7465 **Macrophage Expression of Hypoxia-Inducible Factor-1 α Suppresses T-Cell Function and Promotes Tumor Progression**

Andrew L. Doedens, Christian Stockmann, Mark P. Rubinstein, Debbie Liao, Na Zhang, David G. DeNardo, Lisa M. Coussens, Michael Karin, Ananda W. Goldrath, and Randall S. Johnson

Précis: Findings define a fundamental mechanism through which tumor-associated macrophages are educated to suppress T-cell activation in the tumor microenvironment.

7476 **A Galectin-3 Ligand Corrects the Impaired Function of Human CD4 and CD8 Tumor-Infiltrating Lymphocytes and Favors Tumor Rejection in Mice**

Nathalie Demotte, Grégoire Wieërs, Patrick Van Der Smissen, Muriel Moser, Christopher Schmidt, Kris Thielemans, Jean-Luc Squifflet, Birgit Weynand, Javier Carrasco, Christophe Lurquin, Pierre J. Courttoy, and Pierre van der Bruggen

Précis: Ligands for a cell surface glycoprotein that promotes tumoral immune escape can act as cancer vaccine adjuvants that improve antitumor responses.

MOLECULAR AND CELLULAR PATHOBIOLOGY

7489 **CAV1 Inhibits Metastatic Potential in Melanomas through Suppression of the Integrin/Src/FAK Signaling Pathway**

Casey Trimmer, Diana Whitaker-Menezes, Gloria Bonuccelli, Janet N. Milliman, Kristin M. Daumer, Andrew E. Aplin, Richard G. Pestell, Federica Sotgia, Michael P. Lisanti, and Franco Capozza

Précis: Findings suggest a mechanism through which caveolin-1 can mediate antimetastatic effects in melanoma.

7500 **Epidermal Growth Factor Receptor Expression Identifies Functionally and Molecularly Distinct Tumor-Initiating Cells in Human Glioblastoma Multiforme and Is Required for Gliomagenesis**

Stefania Mazzoleni, Letterio S. Politi, Mauro Pala, Manuela Cominelli, Alberto Franzin, Lucia Sergi Sergi, Andrea Falini, Michele De Palma, Alessandro Bulfone, Pietro L. Poliani, and Rossella Galli

Précis: Findings argue that EGFR-targeted therapies being tested against glioblastoma must take into account non-responder EGFR-negative tumor initiating cells that can thwart therapeutic responses.

7514 **Nongenomic Effects of Cisplatin: Acute Inhibition of Mechanosensitive Transporters and Channels without Actin Remodeling**

Nina Milosavljevic, Christophe Duranton, Nadir Djerbi, Pierre Henri Puech, Pierre Gounon, Dominique Lagadic-Gossmann, Marie Thérèse Dimanche-Boitrel, Cyril Rauch, Michel Tauc, Laurent Counillon, and Mallorie Poët

Précis: Attention to the basis for chemotherapy side effects, a major issue in cancer survivors, is an increasingly important goal for laboratory researchers as advances in clinical care are made.

7523 **Interaction with Vascular Endothelium Enhances Survival in Primary Chronic Lymphocytic Leukemia Cells via NF-κB Activation and *De novo* Gene Transcription**

Andrea G.S. Buggins, Chris Pepper, Piers E.M. Patten, Saman Hewamana, Satyen Gohil, Jane Moorhead, Najeem'deen Folarin, Deborah Yallop, N. Shaun B. Thomas, Ghulam J. Mufti, Chris Fegan, and Stephen Devereux

Précis: Findings show how chronic lymphocytic leukemia cells receive important survival signals through interactions with endothelial cells in blood vessels.

7553 **Image-Guided Breast Tumor Therapy Using a Small Interfering RNA Nanodrug**

Mohanraja Kumar, Mehmet Yigit, Guangping Dai, Anna Moore, and Zdravka Medarova

Précis: Study offers preclinical validation of a generalizable and imageable siRNA therapeutic for cancer treatment, an exciting area for clinical investigation.

7562 **Novel Matrix Metalloproteinase Inhibitor [¹⁸F]Marimastat-Aryltrifluoroborate as a Probe for *In vivo* Positron Emission Tomography Imaging in Cancer**

Ulrich auf dem Keller, Caroline L. Bellac, Ying Li, Yuanmei Lou, Philipp F. Lange, Richard Ting, Curtis Harwig, Reinhild Kappelhoff, Shoukat Dedhar, Michael J. Adam, Thomas J. Ruth, François Bénard, David M. Perrin, and Christopher M. Overall

Précis: Study describes a novel shelf-stable bioconjugate that can be readily converted to a PET probe for *in vivo* cancer imaging studies.

7570 **AXL Is an Essential Factor and Therapeutic Target for Metastatic Ovarian Cancer**

Erinn B. Rankin, Katherine C. Fuh, Tiffany E. Taylor, Adam J. Krieg, Margaret Musser, Jenny Yuan, Kevin Wei, Calvin J. Kuo, Teri A. Longacre, and Amato J. Giaccia

Précis: Findings offer a genetic validation and a candidate biologic therapy for a cell survival kinase that may be effective in most patients diagnosed with metastatic ovarian cancer.

7580 ***MET* and *KRAS* Gene Amplification Mediates Acquired Resistance to *MET* Tyrosine Kinase Inhibitors**

Virna Cepero, J. Rafael Sierra, Simona Corso, Elena Ghiso, Laura Casorzo, Tim Perera, Paolo Maria Comoglio, and Silvia Giordano

Précis: Findings offer initial preclinical evidence for resistance mechanisms that may arise to *MET* kinase inhibitors, which have begun clinical trials.

PREVENTION AND EPIDEMIOLOGY

7534 **Circulating Levels of the Innate and Humoral Immune Regulators CD14 and CD23 Are Associated with Adult Glioma**

Mi Zhou, Joseph L. Wiemels, Paige M. Bracci, Margaret R. Wrensch, Lucie S. Mccoy, Terri Rice, Jennette D. Sison, Joseph S. Patoka, and John K. Wiencke

Précis: Findings strengthen evidence of a clinical inverse correlation between allergies and glioma susceptibility, supporting a particular role for immunoregulatory proteins in brain cancer development.

7543 **Glucuronidation Genotypes and Nicotine Metabolic Phenotypes: Importance of Functional UGT2B10 and UGT2B17 Polymorphisms**

Gang Chen, Nino E. Giambrone, Jr., Douglas F. Dluzen, Joshua E. Muscat, Arthur Berg, Carla J. Gallagher, and Philip Lazarus

Précis: Identification of genotype-phenotype associations in the nicotine metabolism pathway has potential applications in risk assessment and prevention of smoking-related cancers.

7591 **Anti- α v Integrin Monoclonal Antibody Intetumumab Enhances the Efficacy of Radiation Therapy and Reduces Metastasis of Human Cancer Xenografts in Nude Rats**

Shoucheng Ning, Junqiang Tian, Deborah J. Marshall, and Susan J. Knox

Précis: Results offer preclinical proof of concept that an anti-integrin approach can enhance radiotherapeutic responses and reduce metastasis without increasing side effects.

7600 **A Bispecific Antibody-IFN α 2b Immunocytokine Targeting CD20 and HLA-DR Is Highly Toxic to Human Lymphoma and Multiple Myeloma Cells**

Edmund A. Rossi, Diane L. Rossi, Rhona Stein, David M. Goldenberg, and Chien-Hsing Chang

Précis: A novel bispecific immunocytokine which directs dimeric interferon-alpha to the cell surface immune molecules CD20 and HLA-DR may be ideal to eradicate myeloma stem cells.

7610 **Zoledronic Acid as a New Adjuvant Therapeutic Strategy for Ewing's Sarcoma Patients**

Guillaume A. Odri, Sophie Dumoucel, Gaëlle Picarda, Séverine Battaglia, François Lamoureux, Nadège Corradini, Julie Rousseau, Franck Tirode, Karine Laud, Olivier Delattre, François Gouin, Dominique Heymann, and Françoise Redini

Précis: Results offer preclinical proof of concept for the use of an approved anti-osteoporosis drug as an adjuvant for chemotherapeutic management of a primary bone tumor.

7620 **Liver Cancer Protease Activity Profiles Support Therapeutic Options with Matrix Metalloproteinase-Activatable Oncolytic Measles Virus**

Michael D. Mühlebach, Thomas Schaser, Martina Zimmermann, Sorin Armeanu, Kay-Martin O. Hanschmann, Roberto Cattaneo, Michael Bitzer, Ulrich M. Lauer, Klaus Cichutek, and Christian J. Buchholz

Précis: A targeting strategy to improve the specificity of an oncolytic measles virus is described, based on characteristics of individual human patient tumor or adjacent tissue samples.

7630 **GP369, an FGFR2-IIIb-Specific Antibody, Exhibits Potent Antitumor Activity against Human Cancers Driven by Activated FGFR2 Signaling**

Ailin Bai, Kristan Meetze, Nhi Y. Vo, Sriram Kollipara, Elizabeth K. Mazsa, William M. Winston, Solly Weiler, Laura L. Poling, Ting Chen, Nesreen S. Ismail, Jinwei Jiang, Lorena Lerner, Jenó Gyuris, and Zhigang Weng

Précis: Study defines an FGF receptor 2 isoform as a key player in human tumorigenesis, also offering preclinical proof of concept for the beneficial use of FGFR2 antibodies in cancer treatment.

TUMOR AND STEM CELL BIOLOGY

7640 **Hepatocyte Nuclear Factor 4 α Suppresses the Development of Hepatocellular Carcinoma**

Bei-Fang Ning, Jin Ding, Chuan Yin, Wei Zhong, Kun Wu, Xin Zeng, Wen Yang, Yue-Xiang Chen, Jun-Ping Zhang, Xin Zhang, Hong-Yang Wang, and Wei-Fen Xie

Précis: Manipulating the expression or action of a core differentiation-determining transcription factor may offer promising new strategies for the prevention or treatment of hepatocellular carcinoma.

7652 **Tumor Antigen Acrosin Binding Protein Normalizes Mitotic Spindle Function to Promote Cancer Cell Proliferation**

Angelique W. Whitehurst, Yang Xie, Scott C. Purinton, Kathryn M. Cappell, Jackie T. Swanik, Brittany Larson, Luc Girard, John O. Schorge, and Michael A. White

Précis: ACRBP expression modulates ovarian cancer chemoresponsiveness by supporting bipolar mitotic spindle assembly.

7662 **Cancer-Related Epigenome Changes Associated with Reprogramming to Induced Pluripotent Stem Cells**

Joyce E. Ohm, Prashant Mali, Leander Van Neste, David M. Berman, Liang Liang, Kurinji Pandiyan, Kimberly J. Briggs, Wei Zhang, Pedram Argani, Brian Simons, Wayne Yu, William Matsui, Wim Van Criekinge, Feyruz V. Rassool, Elias Zambidis, Kornel E. Schuebel, Leslie Cope, Jonathan Yen, Helai P. Mohammad, Linzhao Cheng, and Stephen B. Baylin

Précis: Genome-wide strategies to identify cancer-related features and epigenetic abnormalities that arise early during reprogramming and persist in induced pluripotent stem cells.

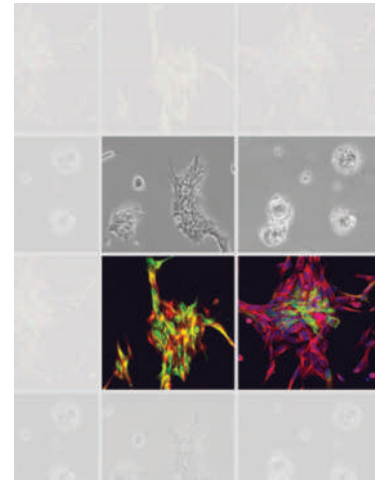
- 7674 **E-Cadherin/p120-Catenin and Tetraspanin Co-029 Cooperate for Cell Motility Control in Human Colon Carcinoma**
Céline Greco, Marie-Pierre Bralet, Naouel Ailane, Anne Dubart-Kupperschmitt, Eric Rubinstein, François Le Naour, and Claude Boucheix
- Précis: Cell surface tetraspanins that associate with integrins may be needed to support the invasive motility of cancer cells after epithelial-mesenchyme transition.*
- 7684 **Activation of Murine Double Minute 2 by Akt in Mammary Epithelium Delays Mammary Involution and Accelerates Mammary Tumorigenesis**
Xiaoyun Cheng, Weiya Xia, Jer-Yen Yang, Jennifer L. Hsu, Jing-Yu Lang, Chao-Kai Chou, Yi Du, Hui-Lung Sun, Shannon L. Wyszomierski, Gordon B. Mills, William J. Muller, Dihua Yu, and Mien-Chie Hung
- Précis: An anti-apoptotic signaling pathway proposed to contribute to breast cancer development is needed for both normal glandular development as well as breast tumorigenesis.*
- 7690 **Aggressive Fibromatosis (Desmoid Tumor) Is Derived from Mesenchymal Progenitor Cells**
Colleen Wu, Saied Nik-Amini, Puvindran Nadesan, William L. Stanford, and Benjamin A. Alman
- Précis: Findings reveal the cellular origin of tumors which are the major cause of mortality in patients harboring germline mutations in the tumor suppressor gene APC.*
- 7699 **Inhibition of Autophagy Enhances Anticancer Effects of Atorvastatin in Digestive Malignancies**
Pei-Ming Yang, Yuan-Ling Liu, Yi-Chu Lin, Chia-Tung Shun, Ming-Shiang Wu, and Ching-Chow Chen
- Précis: Results suggest that a combination of statins and autophagy inhibitors could improve the treatment of liver or colon cancer.*
- 7710 **Implication of Metastasis Suppressor NM23-H1 in Maintaining Adherens Junctions and Limiting the Invasive Potential of Human Cancer Cells**
Mathieu Boissan, Oliver De Wever, Floria Lizarraga, Dominique Wendum, Renaud Poincloux, Nicolas Chignard, Christèle Desbois-Mouthon, Sylvia Dufour, Béatrice Nawrocki-Raby, Philippe Birembaut, Marc Bracke, Philippe Chavrier, Christian Gespach, and Marie-Lise Lacombe
- Précis: Findings describe an important mechanism for control of cell-cell adhesion and cell migration during early stages of the invasive program in epithelial cancers, which acts as a barrier to conversion of in situ carcinoma to invasive disease.*
- 7723 **Image-Based Chemical Screening Identifies Drug Efflux Inhibitors in Lung Cancer Cells**
Xiaofeng Xia, Jian Yang, Fuhai Li, Ying Li, Xiaobo Zhou, Yue Dai, and Stephen T.C. Wong
- Précis: Findings define a high-throughput screening system to identify compounds that can blunt multidrug resistance based on activation of drug efflux mechanisms.*

CORRECTIONS

- 7734 **Correction: Potential for Targeting the Fibroblast Growth Factor Receptors in Breast Cancer**
- 7734 **Correction: 6-Thioguanine Selectively Kills BRCA2-Defective Tumors and Overcomes PARP Inhibitor Resistance**

ABOUT THE COVER

Under proliferative conditions *in vitro*, epidermal growth factor receptor (EGFR)-positive cancer stem cell (CSC) cultures transduced with small hairpin RNA (shRNA) against EGFR displayed dramatic morphologic changes, with neurospheres becoming highly adhesive and cells appearing well differentiated (right). Consistently, the frequency of glial fibrillary acidic protein-positive astrocyte-like cells in shRNA-transduced CSCs was significantly increased as compared to that of controls (left). Tuj1, red; GFAP, green; merge, yellow; TOPRO-3, dark blue. Magnifications: top, 200x; bottom, 400x. For details see the article by Mazzoleni and colleagues on page 7500 of this issue.



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