

## REVIEWS

- 431 | **Defective Mismatch Repair, Microsatellite Mutation Bias, and Variability in Clinical Cancer Phenotypes**  
Sandeep N. Shah, Suzanne E. Hile, and Kristin A. Eckert
- 436 | **The *High Mobility Group A1* Gene: Transforming Inflammatory Signals into Cancer?**  
Linda M.S. Resar

## PERSPECTIVE

- 440 | **Drug Combination Studies and Their Synergy Quantification Using the Chou-Talalay Method**  
Ting-Chao Chou

## PRIORITY REPORT

- 447 | **Genetic Analysis of Transforming Events That Convert Chronic Myeloproliferative Neoplasms to Leukemias**  
Omar Abdel-Wahab, Taghi Manshouri, Jay Patel, Kelly Harris, JinJuan Yao, Cyrus Hedvat, Adriana Heguy, Carlos Bueso-Ramos, Hagop Kantarjian, Ross L. Levine, and Srdan Verstovsek

## CLINICAL STUDIES

- 453 | **Reversing *HoxA9* Oncogene Activation by PI3K Inhibition: Epigenetic Mechanism and Prognostic Significance in Human Glioblastoma**  
Bruno M. Costa, Justin S. Smith, Ying Chen, Justin Chen, Heidi S. Phillips, Kenneth D. Aldape, Giuseppe Zardo, Janice Nigro, C. David James, Jane Fridlyand, Rui M. Reis, and Joseph F. Costello

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 463 | **Predicting Outcomes in Cervical Cancer: A Kinetic Model of Tumor Regression during Radiation Therapy**  
Zhibin Huang, Nina A. Mayr, William T.C. Yuh, Simon S. Lo, Joseph F. Montebello, John C. Grecula, Lanchun Lu, Kaile Li, Hualin Zhang, Nilendu Gupta, and Jian Z. Wang

## MICROENVIRONMENT AND IMMUNOLOGY

- 471 | **Characterization of Phosphoglycerate Kinase-1 Expression of Stromal Cells Derived from Tumor Microenvironment in Prostate Cancer Progression**  
Jianhua Wang, Gigi Ying, Jingchen Wang, Younghun Jung, Jian Lu, Jiang Zhu, Kenneth J. Pienta, and Russell S. Taichman
- 481 | **Natural Killer Cell Cytotoxicity Is Suppressed by Exposure to the Human NKG2D Ligand MICA\*008 That Is Shed by Tumor Cells in Exosomes**  
Omodele Ashiru, Philippe Boutet, Lola Fernández-Messina, Sonia Agüera-González, Jeremy N. Skepper, Mar Valés-Gómez, and Hugh T. Reyburn
- 490 | **Opposing Effects of Toll-like Receptor (TLR3) Signaling in Tumors Can Be Therapeutically Uncoupled to Optimize the Anticancer Efficacy of TLR3 Ligands**  
Rosa Conforti, Yuting Ma, Yannis Morel, Carine Paturel, Magali Terme, Sophie Viaud, Bernard Ryffel, Maria Ferrantini, Ravindra Uppaluri, Robert Schreiber, Christophe Combadière, Nathalie Chaput, Fabrice André, Guido Kroemer, and Laurence Zitvogel

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 501 **Myocardin Functions as an Effective Inducer of Growth Arrest and Differentiation in Human Uterine Leiomyosarcoma Cells**  
Yasunori Kimura, Tsuyoshi Morita, Ken'ichiro Hayashi, Tsuneharu Miki, and Kenji Sobue
- 512 **Oncogenic *BRAF* Mutation with *CDKN2A* Inactivation Is Characteristic of a Subset of Pediatric Malignant Astrocytomas**  
Joshua D. Schiffman, J. Graeme Hodgson, Scott R. VandenBerg, Patrick Flaherty, Mei-Yin C. Polley, Mamie Yu, Paul G. Fisher, David H. Rowitch, James M. Ford, Mitchel S. Berger, Hanlee Ji, David H. Gutmann, and C. David James
- 520 **Insertional Mutagenesis in Mice Deficient for *p15<sup>Ink4b</sup>*, *p16<sup>Ink4a</sup>*, *p21<sup>Cip1</sup>*, and *p27<sup>Kip1</sup>* Reveals Cancer Gene Interactions and Correlations with Tumor Phenotypes**  
Jaap Kool, Anthony G. Uren, Carla P. Martins, Daoud Sie, Jeroen de Ridder, Geoffrey Turner, Miranda van Uiter, Konstantin Matentzoglou, Wendy Lagcher, Paul Krimpenfort, Jules Gadiot, Colin Pritchard, Jack Lenz, Anders H. Lund, Jos Jonkers, Jane Rogers, David J. Adams, Lodewyk Wessels, Anton Berns, and Maarten van Lohuizen
- 532 **Transcriptional Autoregulation by *BRCA1***  
Adriana De Siervi, Paola De Luca, Jung S. Byun, Li Jun Di, Temesgen Fufa, Cynthia M. Haggerty, Elba Vazquez, Cristian Moiola, Dan L. Longo, and Kevin Gardner
- 543 ***SLIT2* Attenuation during Lung Cancer Progression Deregulates  $\beta$ -Catenin and E-Cadherin and Associates with Poor Prognosis**  
Ruo-Chia Tseng, Shih-Hua Lee, Han-Shui Hsu, Ben-Han Chen, Wan-Ching Tsai, Ching Tzao, and Yi-Ching Wang
- 552 **Estimating *CDKN2A* Carrier Probability and Personalizing Cancer Risk Assessments in Hereditary Melanoma Using MelaPRO**  
Wenyi Wang, Kristin B. Niendorf, Devanshi Patel, Amanda Blackford, Fabio Marroni, Arthur J. Sober, Giovanni Parmigiani, and Hensin Tsao

- 560 **Cell-Free Nucleic Acids Circulating in the Plasma of Colorectal Cancer Patients Induce the Oncogenic Transformation of Susceptible Cultured Cells**  
Dolores C. García-Olmo, Carolina Domínguez, Mariano García-Arranz, Phillipe Anker, Maurice Stroun, José M. García-Verdugo, and Damián García-Olmo

## PREVENTION AND EPIDEMIOLOGY

- 568 **Multivitamins, Folate, and Green Vegetables Protect against Gene Promoter Methylation in the Aerodigestive Tract of Smokers**  
Christine A. Stidley, Maria A. Picchi, Shuguang Leng, Randy Willink, Richard E. Crowell, Kristina G. Flores, Huining Kang, Tim Byers, Frank D. Gilliland, and Steven A. Belinsky
- 575 **Use of Four Biomarkers to Evaluate the Risk of Breast Cancer Subtypes in the Women's Contraceptive and Reproductive Experiences Study**  
Huiyan Ma, Yaping Wang, Jane Sullivan-Halley, Linda Weiss, Polly A. Marchbanks, Robert Spirtas, Giske Ursin, Ronald T. Burkman, Michael S. Simon, Kathleen E. Malone, Brian L. Strom, Jill A. McDonald, Michael F. Press, and Leslie Bernstein

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 588 **Sym004: A Novel Synergistic Anti-Epidermal Growth Factor Receptor Antibody Mixture with Superior Anticancer Efficacy**  
Mikkel Wandahl Pedersen, Helle Jane Jacobsen, Klaus Koefoed, Adam Hey, Charles Pyke, John Sørensen Haurum, and Michael Kragh
- 598 **Myxoma Virus Virotherapy for Glioma in Immunocompetent Animal Models: Optimizing Administration Routes and Synergy with Rapamycin**  
XueQing Lun, Tommy Alain, Franz J. Zemp, Hongyuan Zhou, Masmudur M. Rahman, Mark G. Hamilton, Grant McFadden, John Bell, Donna L. Senger, and Peter A. Forsyth

- 609 **Apoptotic Sensitivity of Colon Cancer Cells to Histone Deacetylase Inhibitors Is Mediated by an Sp1/Sp3-Activated Transcriptional Program Involving Immediate-Early Gene Induction**  
Andrew J. Wilson, Anderly C. Chueh, Lars Tögel, Georgia A. Corner, Naseem Ahmed, Sanjay Goel, Do-Sun Byun, Shannon Nasser, Michele A. Houston, Minaxi Jhawer, Helena J.M. Smartt, Lucas B. Murray, Courtney Nicholas, Barbara G. Heerdt, Diego Arango, Leonard H. Augenlicht, and John M. Mariadason
- 621 **Beyond Rapalog Therapy: Preclinical Pharmacology and Antitumor Activity of WYE-125132, an ATP-Competitive and Specific Inhibitor of mTORC1 and mTORC2**  
Ker Yu, Celine Shi, Lourdes Toral-Barza, Judy Lucas, Boris Shor, Jae Eun Kim, Wei-Guo Zhang, Robert Mahoney, Christine Gaydos, LuAnna Tardio, Sung Kyoo Kim, Roger Conant, Kevin Curran, Joshua Kaplan, Jeroen Verheijen, Semiramis Ayril-Kaloustian, Tarek S. Mansour, Robert T. Abraham, Arie Zask, and James J. Gibbons
- 632 **Targeting Specific Regions of the Notch3 Ligand-Binding Domain Induces Apoptosis and Inhibits Tumor Growth in Lung Cancer**  
Luping Lin, Ray Mernaugh, Fuming Yi, David Blum, David P. Carbone, and Thao P. Dang
- 639 **Identification of the Receptor Tyrosine Kinase c-Met and Its Ligand, Hepatocyte Growth Factor, as Therapeutic Targets in Clear Cell Sarcoma**  
Ian J. Davis, Andrew W. McFadden, Yixiang Zhang, Angela Coxon, Teresa L. Burgess, Andrew J. Wagner, and David E. Fisher
- 646 **Chemopreventive Agent 3,3'-Diindolylmethane Selectively Induces Proteasomal Degradation of Class I Histone Deacetylases**  
Yongming Li, Xia Li, and Bin Guo
- 655 **Identification of USP18 as an Important Regulator of the Susceptibility to IFN- $\alpha$  and Drug-Induced Apoptosis**  
Harish Potu, Andrea Sgorbissa, and Claudio Brancolini
- 666 **The Somatostatin Analogue Octreotide Confers Sensitivity to Rapamycin Treatment on Pituitary Tumor Cells**  
Vesna Cerovac, Jose Monteserin-Garcia, Hadara Rubinfeld, Michael Buchfelder, Marco Losa, Tullio Florio, Marcelo Paez-Pereda, Günter K. Stalla, and Marily Theodoropoulou
- TUMOR AND STEM CELL BIOLOGY**
- 675 **Oncogenic B-Raf<sup>V600E</sup> Induces Spindle Abnormalities, Supernumerary Centrosomes, and Aneuploidy in Human Melanocytic Cells**  
Yongping Cui, Meghan K. Borysova, Joseph O. Johnson, and Thomas M. Guadagno
- 685 **Prognosis of Hormone-Dependent Breast Cancers: Implications of the Presence of Dysfunctional Transcriptional Networks Activated by Insulin via the Immune Transcription Factor T-bet**  
Kasi McCune, Poornima Bhat-Nakshatri, Mangesh A. Thorat, Kenneth P. Nephew, Sunil Badve, and Harikrishna Nakshatri
- 697 **Modulation of T-Cell Activation by Malignant Melanoma Initiating Cells**  
Tobias Schatton, Ute Schütte, Natasha Y. Frank, Qian Zhan, André Hoerning, Susanne C. Robles, Jun Zhou, F. Stephen Hodi, Giulio C. Spagnoli, George F. Murphy, and Markus H. Frank
- 709 **Regulation of Breast Cancer Stem Cell Activity by Signaling through the Notch4 Receptor**  
Hannah Harrison, Gillian Farnie, Sacha J. Howell, Rebecca E. Rock, Spyros Stylianou, Keith R. Brennan, Nigel J. Bundred, and Robert B. Clarke
- 719 **The AC133 Epitope, but not the CD133 Protein, Is Lost upon Cancer Stem Cell Differentiation**  
Kristel Kemper, Martin R. Sprick, Martijn de Bree, Alessandro Scopelliti, Louis Vermeulen, Maarten Hoek, Jurrit Zeilstra, Steven T. Pals, Huseyin Mehmet, Giorgio Stassi, and Jan Paul Medema
- 730 **ETS-1 Oncogenic Activity Mediated by Transforming Growth Factor  $\alpha$**   
Chet E. Holterman, Aleksandra Franovic, Josianne Payette, and Stephen Lee

- 741 **Insulin-Mediated Acceleration of Breast Cancer Development and Progression in a Nonobese Model of Type 2 Diabetes**  
Ruslan Novosyadlyy, Danielle E. Lann, Archana Vijayakumar, Anne Rowzee, Deborah A. Lazzarino, Yvonne Fierz, Joan M. Carboni, Marco M. Gottardis, Patricia A. Pennisi, Alfredo A. Molinolo, Naamit Kurshan, Wilson Mejia, Stefania Santopietro, Shoshana Yakar, Teresa L. Wood, and Derek LeRoith
- 752 **NF- $\kappa$ B-Dependent Plasticity of the Epithelial to Mesenchymal Transition Induced by *Von Hippel-Lindau* Inactivation in Renal Cell Carcinomas**  
Allan J. Pantuck, Jiabin An, Huiren Liu, and Matthew B. Rettig
- 762 **Silencing of SPRY1 Triggers Complete Regression of Rhabdomyosarcoma Tumors Carrying a Mutated *RAS* Gene**  
Gerben Schaaf, Mohamed Hamdi, Danny Zwijnenburg, Arjan Lakeman, Dirk Geerts, Rogier Versteeg, and Marcel Kool
- 772 **SIP<sub>2</sub>, the G Protein-Coupled Receptor for Sphingosine-1-Phosphate, Negatively Regulates Tumor Angiogenesis and Tumor Growth *In vivo* in Mice**  
Wa Du, Noriko Takuwa, Kazuaki Yoshioka, Yasuo Okamoto, Koichi Gonda, Kazushi Sugihara, Akiyoshi Fukamizu, Masahide Asano, and Yoh Takuwa
- 782 **E2F8 Contributes to Human Hepatocellular Carcinoma via Regulating Cell Proliferation**  
Qing Deng, Qun Wang, Wei-Ying Zong, Da-Li Zheng, Yi-Xin Wen, Ke-Sheng Wang, Xiao-Mei Teng, Xin Zhang, Jian Huang, and Ze-Guang Han
- 792 **Matrix Metalloproteinase-9 Functions as a Tumor Suppressor in Colitis-Associated Cancer**  
Pallavi Garg, Dittakavi Sarma, Sabrina Jeppsson, Neal R. Patel, Andrew T. Gewirtz, Didier Merlin, and Shanthi V. Sitaraman
- 802 **A Single Nucleotide Change in the Mouse Genome Accelerates Breast Cancer Progression**  
Nina Seitzer, Thomas Mayr, Sylvia Streit, and Axel Ullrich
- 813 **JNK1 Mediates Degradation HIF-1 $\alpha$  by a VHL-Independent Mechanism that Involves the Chaperones Hsp90/Hsp70**  
Dongyun Zhang, Jingxia Li, Max Costa, Jimin Gao, and Chuanshu Huang
- 824 **HEF1 Is a Crucial Mediator of the Proliferative Effects of Prostaglandin E<sub>2</sub> on Colon Cancer Cells**  
Dianren Xia, Vijaykumar R. Holla, Dingzhi Wang, David G. Menter, and Raymond N. DuBois
- 832 **p38 Mitogen-Activated Protein Kinase-Driven MAPKAPK2 Regulates Invasion of Bladder Cancer by Modulation of MMP-2 and MMP-9 Activity**  
Binod Kumar, Sweaty Koul, Jane Petersen, Lakshmipathi Khandrika, Jeong S. Hwa, Randall B. Meacham, Shandra Wilson, and Hari K. Koul
- 842 **Discovery and Mechanistic Characterization of a Novel Selective Nuclear Androgen Receptor Exporter for the Treatment of Prostate Cancer**  
Ramesh Narayanan, Muralimohan Yepuru, Adam T. Szafran, Maria Szwarc, Casey E. Bohl, Natalie L. Young, Duane D. Miller, Michael A. Mancini, and James T. Dalton

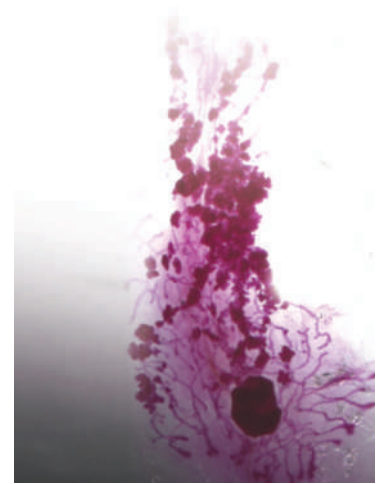
## CORRECTIONS

- 852 **Correction: Transforming Growth Factor  $\alpha$  Expression Drives Constitutive Epidermal Growth Factor Receptor Pathway Activation and Sensitivity to Gefitinib (Iressa) in Human Pancreatic Cancer Cell Lines**
- 853 **Correction: Adjuvant Hormonal Therapy for Breast Cancer and Risk of Hormone Receptor-Specific Subtypes of Contralateral Breast Cancer**
- 854 **Correction: Positive Cross-Talk between Estrogen Receptor and NF- $\kappa$ B in Breast Cancer**

---

## ABOUT THE COVER

Numerous epidemiological studies indicate that obesity and type 2 diabetes significantly increase breast cancer risk and mortality. The molecular mechanisms implicated in this association remain poorly understood. By employing a nonobese model of type 2 diabetes, Novosyadlyy and colleagues show that type 2 diabetes accelerates mammary gland development, formation of hyperplastic precancerous lesions, and malignant tumor growth independent of obesity. Furthermore, the authors demonstrate that hyperinsulinemia acting through the insulin and IGF-I receptors is a key pathophysiological mechanism promoting tumor development in the context of type 2 diabetes. Finally, the authors propose that interventions aimed at reducing insulin levels and signaling may delay the onset of cancer in patients with type 2 diabetes and will have an enormously positive public health impact. For details, see the article by Novosyadlyy and colleagues on page 741 of this issue.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

## 70 (2)

*Cancer Res* 2010;70:431-854.

**Updated version** Access the most recent version of this article at:  
<http://cancerres.aacrjournals.org/content/70/2>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/70/2>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.