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# Cancer Research

August 1, 2011 • Volume 71 • Number 15

## BREAKING ADVANCES

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## REVIEWS

- 5057 | **Hedgehog Fights Back: Mechanisms of Acquired Resistance against Smoothed Antagonists**  
Ciara Metcalfe and Frederic J. de Sauvage
- 5062 | **Chemotherapeutic Resistance: Surviving Stressful Situations**  
Luke A. Gilbert and Michael T. Hemann

## PRIORITY REPORTS

- 5067 | **Combinatorial Treatments That Overcome PDGFR $\beta$ -Driven Resistance of Melanoma Cells to <sup>V600E</sup>B-RAF Inhibition**  
Hubing Shi, Xiangju Kong, Antoni Ribas, and Roger S. Lo
- Précis:* This study illustrates the great importance of the interplay between clinical and laboratory-based research in responding rapidly to the inevitable problem of acquired resistance arising in the development of any new targeted treatment for cancer.
- 5075 | **Mechanical Stiffness Grades Metastatic Potential in Patient Tumor Cells and in Cancer Cell Lines**  
Vinay Swaminathan, Karthikeyan Mythreya, E. Tim O'Brien, Andrew Berchuck, Gerard C. Blobe, and Richard Superfine

*Précis:* Findings provide the first demonstration of the power law relation between the stiffness and the invasiveness of cancer cells and show that mechanical phenotypes, which are directly impacted by the state and architecture of the cytoskeleton, can be used to grade the metastatic potential of cell populations.

## CLINICAL STUDIES

- 5081 | **Keap1 Mutations and Nrf2 Pathway Activation in Epithelial Ovarian Cancer**  
Panagiotis A. Konstantinopoulos, Dimitrios Spentzos, Elena Fountzilas, Nancy Francoeur, Srisowmya Sanisetty, Alexandros P. Grammatikos, Jonathan L. Hecht, and Stephen A. Cannistra

*Précis:* Findings reveal a key molecular determinant of resistance to platinum-based chemotherapy and poor clinical outcome in patients with epithelial ovarian cancers.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 5090 | **Tumor Microenvironment–Derived Proteins Dominate the Plasma Proteome Response during Breast Cancer Induction and Progression**  
Sharon J. Pitteri, Karen S. Kelly-Spratt, Kay E. Gurley, Jacob Kennedy, Tina Busald Buson, Alice Chin, Hong Wang, Qing Zhang, Chee-Hong Wong, Lewis A. Chodosh, Peter S. Nelson, Samir M. Hanash, and Christopher J. Kemp

*Précis:* Dynamic interactions between tumor cells and their host microenvironment are reflected by changes in the plasma proteome, offering new opportunities for cancer diagnosis.

## MICROENVIRONMENT AND IMMUNOLOGY

- 5101 | **Myeloid-Derived Suppressor Cell Inhibition of the IFN Response in Tumor-Bearing Mice**  
Bethany L. Mundy-Bosse, Gregory B. Lesinski, Alena C. Jaime-Ramirez, Kristen Benninger, Mahmood Khan, Periannan Kuppusamy, Kristan Guenterberg, Sri Vidya Kondadasula, Abhik Ray Chaudhury, Krista M. La Perle, Melanie Kreiner, Gregory Young, Denis C. Guttridge, and William E. Carson, III

*Précis:* Myeloid derived suppressor cells blunt immune cell responsiveness to interferons by producing reactive nitrogen species, which attenuates interferon signaling in immune cells of tumor-bearing animals.

5111 **PD-1/PD-L1 Interactions Contribute to Functional T-Cell Impairment in Patients Who Relapse with Cancer After Allogeneic Stem Cell Transplantation**

Wieger J. Norde, Frans Maas, Willemijn Hobo, Alan Korman, Michael Quigley, Michel G.D. Kester, Konnie Hebeda, J.H. Frederik Falkenburg, Nicolaas Schaap, Theo M. de Witte, Robbert van der Voort, and Harry Dolstra

*Précis:* Findings show how leukemia cells can escape from graft-versus-tumor immune responses, and how interfering with this escape mechanism can restore antitumor immunity and possibly prevent relapses.

5123 **Systemic Cancer Therapy with a Small Molecule Agonist of Toll-like Receptor 7 Can Be Improved by Circumventing TLR Tolerance**

Carole Bourquin, Christian Hotz, Daniel Noerenberg, Andreas Voelkl, Simon Heidegger, Laurin C. Roetzer, Bettina Storch, Nadja Sandholzer, Cornelia Wurzenberger, David Anz, and Stefan Endres

*Précis:* Findings offer insight into a cellular mechanism of immune tolerance that occurs during cancer immunotherapy with a Toll-like receptor agonist and provide a strategy to bypass this tolerance.

5134 **Antibody-Dependent Cell Cytotoxicity Synapses Form in Mice during Tumor-Specific Antibody Immunotherapy**

Pascale Hubert, Adèle Heitzmann, Sophie Viel, André Nicolas, Xavier Sastre-Garau, Pablo Oppezco, Otto Pritsch, Eduardo Osinaga, and Sebastian Amigorena

*Précis:* Findings demonstrate that a therapeutic monoclonal antibody specific for a ubiquitous tumor-associated antigen inhibits tumor growth via antibody-dependent cell toxicity.

5154 **IGFBP-3 Is a Metastasis Suppression Gene in Prostate Cancer**

Hemal H. Mehta, Qinglei Gao, Colette Galet, Vladislava Paharkova, Junxiang Wan, Jonathan Said, Joanne J. Sohn, Gregory Lawson, Pinchas Cohen, Laura J. Cobb, and Kuk-Wha Lee

*Précis:* This study reports the first transgenic mouse model of spontaneous metastatic prostate cancer, a milestone that may help advance studies of progression and treatment at this deadly late stage of disease.

5164 **<sup>18</sup>F-Fluorodeoxy-glucose Positron Emission Tomography Marks MYC-Overexpressing Human Basal-Like Breast Cancers**

Nicolaos Palaskas, Steven M. Larson, Nikolaus Schultz, Evangelia Komisopoulou, Justin Wong, Dan Rohle, Carl Campos, Nicolas Yannuzzi, Joseph R. Osborne, Irina Linkov, Edward R. Kastenhuber, Richard Taschereau, Seema B. Plaisier, Chris Tran, Adriana Heguy, Hong Wu, Chris Sander, Michael E. Phelps, Cameron Brennan, Elisa Port, Jason T. Huse, Thomas G. Graeber, and Ingo K. Mellingerhoff

*Précis:* FDG-PET may be useful as a noninvasive biomarker for therapies that target either the basal-like breast cancer subtype or MYC-overexpressing tumors that rely heavily upon glycolysis and the glutamine pathway.

## PREVENTION AND EPIDEMIOLOGY

5175 **Genetic Variation in an miRNA-1827 Binding Site in MYCL1 Alters Susceptibility to Small-Cell Lung Cancer**

Fang Xiong, Chen Wu, Jiang Chang, Dianke Yu, Binghe Xu, Peng Yuan, Kan Zhai, Jian Xu, Wen Tan, and Dongxin Lin

*Précis:* Findings suggest a broader significance than appreciated previously for the L-MYC gene in development of small cell lung cancer.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

5144 **Inhibition of miR-193a Expression by Max and RXR $\alpha$  Activates K-Ras and PLAU to Mediate Distinct Aspects of Cellular Transformation**

Dimitrios Iliopoulos, Asaf Rotem, and Kevin Struhl

*Précis:* Findings describe a molecular pathway involved in cellular transformation that focuses on miR-193a as a regulator of both tumorigenicity and invasiveness.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

5182 **Combining Betulinic Acid and Mithramycin A Effectively Suppresses Pancreatic Cancer by Inhibiting Proliferation, Invasion, and Angiogenesis**

Yong Gao, Zhiliang Jia, Xiangyu Kong, Qiang Li, David Z. Chang, Daoyan Wei, Xiangdong Le, Shengdong Huang, Liwei Wang, Suyun Huang, and Keping Xie

*Précis:* Findings demonstrate that targeting the transcription factor Sp1 can inhibit pancreatic tumor growth with greater efficacy and fewer side effects than traditional treatment.

- 5194 **BMP4 Promotes Prostate Tumor Growth in Bone through Osteogenesis**  
Yu-Chen Lee, Chien-Jui Cheng, Mehmet A. Bilen, Jing-Fang Lu, Robert L. Satcher, Li-Yuan Yu-Lee, Gary E. Gallick, Sankar N. Maity, and Sue-Hwa Lin  
*Précis:* Osteogenesis is shown to be necessary for prostate cancer progression in bone and inhibition of this process may offer a treatment strategy for bone metastases.
- 5204 **Akt-Dependent Glucose Metabolism Promotes Mcl-1 Synthesis to Maintain Cell Survival and Resistance to Bcl-2 Inhibition**  
Jonathan L. Coloff, Andrew N. Macintyre, Amanda G. Nichols, Tingyu Liu, Catherine A. Gallo, David R. Plas, and Jeffrey C. Rathmell  
*Précis:* Inhibition of glucose metabolism alters expression of a key Bcl-2 family member, sensitizing cancer cells to apoptosis and illustrating how strategies to disrupt glycolysis disruptions may disable tumors.
- 5214 **MicroRNA Replacement Therapy for miR-145 and miR-33a Is Efficacious in a Model of Colon Carcinoma**  
Ahmed Fawzy Ibrahim, Ulrike Weirauch, Maren Thomas, Arnold Grünweller, Roland K. Hartmann, and Achim Aigner  
*Précis:* This study establishes nonviral miRNA replacement therapy for cancer treatment.
- 5225 **Combined Gene Expression Profiling and RNAi Screening in Clear Cell Renal Cell Carcinoma Identify PLK1 and Other Therapeutic Kinase Targets**  
Yan Ding, Dan Huang, Zhongfa Zhang, Josh Smith, David Petillo, Brendan D. Looyenga, Kristin Feenstra, Jeffrey P. MacKeigan, Kyle A. Furge, and Bin T. Teh  
*Précis:* RNAi screening and gene expression profiling reveal new potential therapeutic targets to treat highly aggressive kidney cancers.
- 5235 **Exosome Targeting of Tumor Antigens Expressed by Cancer Vaccines Can Improve Antigen Immunogenicity and Therapeutic Efficacy**  
Ryan B. Rountree, Stefanie J. Mandl, James M. Nachtwey, Katie Dalpozzo, Lisa Do, John R. Lombardo, Peter L. Schoonmaker, Kay Brinkmann, Ulrike Dirmeier, Reiner Laus, and Alain Delcayre  
*Précis:* This study shows how engineering the MVA-BN-PRO vaccine to express its antigens in secreted exosomes could greatly improve its immunotherapeutic activity.
- 5245 **Retinoic Acid Enhances TRAIL-Induced Apoptosis in Cancer Cells by Upregulating TRAIL Receptor 1 Expression**  
Latha Dhandapani, Ping Yue, Suresh S. Ramalingam, Fadlo R. Khuri, and Shi-Yong Sun  
*Précis:* By establishing that retinoic acid can stimulate the proapoptotic activity of TRAIL by upregulating the TRAIL receptor DR4, this study suggests a strategy to augment the anticancer activity of TRAIL being studied in clinical trials.
- 5255 **A Drug Resistance Screen Using a Selective MET Inhibitor Reveals a Spectrum of Mutations That Partially Overlap with Activating Mutations Found in Cancer Patients**  
Ralph Tiedt, Elisa Degenkolbe, Pascal Furet, Brent A. Appleton, Sabrina Wagner, Joseph Schoepfer, Emily Buck, David A. Ruddy, John E. Monahan, Michael D. Jones, Jutta Blank, Dorothea Haasen, Peter Druেকে, Markus Wartmann, Clive McCarthy, William R. Sellers, and Francesco Hofmann  
*Précis:* Drug resistance mutation profiles reported in this manuscript are likely to predict clinical responses to MET kinase inhibitors, a number of which are currently in development.
- 5265 **Overcoming Hypoxia-Induced Apoptotic Resistance through Combinatorial Inhibition of GSK-3 $\beta$  and CDK1**  
Patrick A. Mayes, Nathan G. Dolloff, Colin J. Daniel, J. Judy Liu, Lori S. Hart, Kageaki Kuribayashi, Joshua E. Allen, David I.H. Jee, Jay F. Dorsey, Yingqiu Y. Liu, David T. Dicker, J. Martin Brown, Emma E. Furth, Peter S. Klein, Rosalie C. Sears, and Wafik S. El-Deiry  
*Précis:* Findings elucidate a novel therapeutic strategy to overcome the inherent resistance of hypoxic cancer cells to cell death, by targeting two kinases not previously linked to cell death protection in hypoxic tumor microenvironments.

5276 **Interleukin-1 $\alpha$  Mediates the Antiproliferative Effects of 1,25-Dihydroxyvitamin D<sub>3</sub> in Prostate Progenitor/Stem Cells**  
 Sophia L. Maund, Wendy W. Barclay, Laura D. Hover, Linara S. Axanova, Guangchao Sui, Jason D. Hipp, James C. Fleet, Andrew Thorburn, and Scott D. Cramer

*Précis:* Supporting applications of vitamin D as a chemopreventative agent for prostate cancer, this study shows that the metabolically active form of vitamin D can induce differentiation and senescence of prostate progenitor/stem cells and that its antiproliferative effects rely upon interleukin-1  $\alpha$ .

5287 **PTEN Positively Regulates UVB-Induced DNA Damage Repair**  
 Mei Ming, Li Feng, Christopher R. Shea, Keyoumars Soltani, Baozhong Zhao, Weinong Han, Robert C. Smart, Carol S. Trempus, and Yu-Ying He

*Précis:* Findings explain how failure to repair DNA damage caused by UVB sunlight radiation can cause skin carcinogenesis, due to inactivation of the tumor suppressor PTEN that destroys its key gatekeeper function in supporting DNA repair in the skin.

5296 **IL-8 Signaling Plays a Critical Role in the Epithelial–Mesenchymal Transition of Human Carcinoma Cells**  
 Romaine I. Fernando, Marianne D. Castillo, Mary Litzinger, Duane H. Hamilton, and Claudia Palena

*Précis:* Findings elucidate the role of epithelial-to-mesenchymal transition in the modulation of the tumor microenvironment, suggesting that IL-8 signaling blockades might be very effective at targeting invasive tumor cells.

5307 **ABCB5 Identifies a Therapy-Refractory Tumor Cell Population in Colorectal Cancer Patients**  
 Brian J. Wilson, Tobias Schatton, Qian Zhan, Martin Gasser, Jie Ma, Karim R. Saab, Robin Schanche, Ana-Maria Waaga-Gasser, Jason S. Gold, Qin Huang, George F. Murphy, Markus H. Frank, and Natasha Y. Frank

*Précis:* Findings point to the need to eradicate a particular tumor cell population to improve outcomes in colorectal cancer therapy.

5317 **Cancer Stem Cells in Squamous Cell Carcinoma Switch between Two Distinct Phenotypes That Are Preferentially Migratory or Proliferative**  
 Adrian Biddle, Xiao Liang, Luke Gammon, Bilal Fazil, Lisa J. Harper, Helena Emich, Daniela Elena Costea, and Ian C. Mackenzie

*Précis:* Findings suggest that cancer stem cells can switch their phenotype between two states that can either drive tumor cell proliferation or metastatic dissemination, implying a need for therapeutic approaches that are able to eradicate cancer stem cells in both states.

5327 **ADP-Ribosylarginine Hydrolase Regulates Cell Proliferation and Tumorigenesis**  
 Jiro Kato, Jianfeng Zhu, Chengyu Liu, Mario Stylianou, Victoria Hoffmann, Martin J. Lizak, Connie G. Glasgow, and Joel Moss

*Précis:* Findings point to an important role for posttranslational protein modification by ADP-ribosylation in supporting cell proliferation and tumorigenesis.

5336 **Sequential Activation of Snail and N-Myc Modulates Sonic Hedgehog–Induced Transformation of Neural Cells**  
 Leah E. Colvin Wanshura, Katherine E. Galvin, Hong Ye, Martin E. Fernandez-Zapico, and Cynthia Wetmore

*Précis:* N-Myc activation by a key target of the Sonic Hedgehog signaling pathway may be an essential step information of an aggressive class of pediatric brain tumors, with implications for therapeutic targeting strategies.

5346 **Microvesicles Released from Human Renal Cancer Stem Cells Stimulate Angiogenesis and Formation of Lung Premetastatic Niche**  
 Cristina Grange, Marta Tapparo, Federica Collino, Lorian Vitillo, Christian Damasco, Maria Chiara Deregibus, Ciro Tetta, Benedetta Bussolati, and Giovanni Camussi

*Précis:* Cancer stem cells may promote metastatic progression by secreting a class of microvesicles known as exosomes that can transfer proangiogenic RNAs to endothelial cells and directly stimulate angiogenesis.

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## LETTERS TO THE EDITOR

5357 | **MicroRNA Expression and Outcome in Resected NSCLC—Letter**

Shun-ichiro Kageyama, Yusuke Takagi, Takeshi Sawada, Natsuko Kageyama-Yahara, and Masahiko Shibuya

5358 | **MicroRNA Expression and Outcome in Resected NSCLC—Response**

Johannes Voortman, Aaron J. Schetter, Curtis C. Harris, and Giuseppe Giaccone

## CORRECTIONS

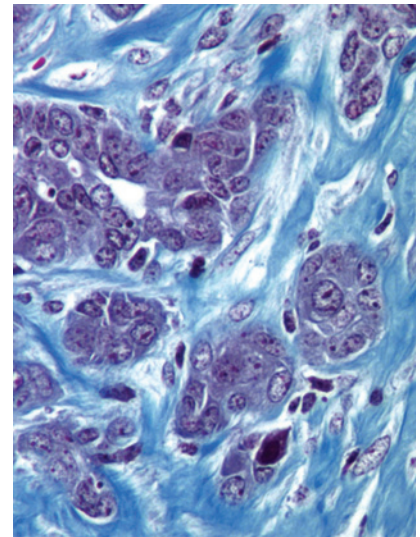
5360 | **Correction: Effects of Carbon Ion Beam on Putative Colon Cancer Stem Cells and Its Comparison with X-rays**

5361 | **Correction: A Requirement of STAT3 DNA Binding Precludes Th-1 Immunostimulatory Gene Expression by NF- $\kappa$ B in Tumors**

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## ABOUT THE COVER

The search for biomarkers of cancer has focused on the tumor cells themselves. Pitteri and colleagues, using an unbiased and in depth proteomic analysis of plasma from a model of Her2/neu driven breast cancer, have identified the signaling between the tumor cells and microenvironment as a primary source of biomarkers. Shown are tumor cells embedded within extensive extracellular collagen matrix stained with trichrome blue. For details, see the article by Pitteri and colleagues on page 5090 of this issue.



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