

# Contents

# Cancer Research

September 15, 2012 • Volume 72 • Number 18

## BREAKING ADVANCES

- 4609 | **Highlights from Recent Cancer Literature**

## REVIEWS

- 4611 | **Androgen Receptor on the Move: Boarding the Microtubule Expressway to the Nucleus**  
Maria Thadani-Mulero, David M. Nanus, and Paraskevi Giannakakou
- 4616 | **Role of the Human High-Affinity Copper Transporter in Copper Homeostasis Regulation and Cisplatin Sensitivity in Cancer Chemotherapy**  
Macus Tien Kuo, Siqing Fu, Niramol Savaraj, and Helen H.W. Chen

## PRIORITY REPORT

- 4622 | **Real-time Monitoring of *In Vivo* Acute Necrotic Cancer Cell Death Induced by Near Infrared Photoimmunotherapy Using Fluorescence Lifetime Imaging**  
Takahito Nakajima, Kohei Sano, Makoto Mitsunaga, Peter L. Choyke, and Hisataka Kobayashi
- Précis:* Findings illustrate how a type of noninvasive fluorescence imaging can be used to monitor antitumor therapeutic effects at very early times before morphological changes become apparent.

## MICROENVIRONMENT AND IMMUNOLOGY

- 4629 | **Hypoxia-Inducible miR-210 Regulates the Susceptibility of Tumor Cells to Lysis by Cytotoxic T Cells**  
Muhammad Zaeem Noman, Stéphanie Buart, Pedro Romero, Sami Ketari, Bassam Janji, Bernard Mari, Fathia Mami-Chouaib, and Salem Chouaib
- Précis:* This seminal study defines a microRNA whose induction links hypoxia to immune escape, providing a new mechanistic understanding of how immunosuppression arises in oxygen-deprived regions of tumors where the most aggressive behaviors evolve.

- 4642 | **NFAT1 Supports Tumor-induced Anergy of CD4<sup>+</sup> T Cells**  
Brian T. Abe, Daniel S. Shin, Enric Mocholi, and Fernando Macian

*Précis:* Results directly implicate CD4<sup>+</sup> T-cell anergy in immune escape, opening the possibility of targeting a transcription factor known to induce T-cell anergy as a general strategy to improve any immunotherapy or immunochemotherapy for cancer treatment.

- 4652 | **Activation of Robo1 Signaling of Breast Cancer Cells by Slit2 from Stromal Fibroblast Restrains Tumorigenesis via Blocking PI3K/Akt/ $\beta$ -Catenin Pathway**  
Po-Hao Chang, Wendy W. Hwang-Verslues, Yi-Cheng Chang, Chun-Chin Chen, Michael Hsiao, Yung-Ming Jeng, King-Jen Chang, Eva Y.-H.P. Lee, Jin-Yuh Shew, and Wen-Hwa Lee
- Précis:* Findings show how stromal fibroblasts can suppress the tumorigenicity of breast cancer cells, offering a potentially broadspectrum marker for clinical prognosis of breast cancers.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4662 | **Platelets and P-Selectin Control Tumor Cell Metastasis in an Organ-Specific Manner and Independently of NK Cells**  
Lucy A. Coupland, Beng H. Chong, and Christopher R. Parish
- Précis:* Prometastatic effects of platelets are organ specific, perhaps explaining the failure of antiplatelet therapy in patients and revealing an unexpected prometastatic role for endothelium-derived P-selectin in lung and liver metastasis.
- 4672 | **Collaboration of Kras and Androgen Receptor Signaling Stimulates EZH2 Expression and Tumor-Propagating Cells in Prostate Cancer**  
Houjian Cai, Sanaz Memarzadeh, Tanya Stoyanova, Zanna Beharry, Andrew S. Kraft, and Owen N. Witte
- Précis:* This study offers mechanistic insights into how prostate cancer progresses to its deadly final stage when metastatic capabilities emerge, revealing how upregulation of a key transcriptional regulator is linked to the generation of cancer progenitor cells that may be crucial at this stage.



4682 ***Ink4a/Arf* Inactivation with Activation of the NF- $\kappa$ B/IL-6 Pathway Is Sufficient to Drive the Development and Growth of Angiosarcoma**

Jinming Yang, Sara Kantrow, Jiqing Sai, Oriana E. Hawkins, Mark Boothby, Gregory D. Ayers, Eric D. Young, Elizabeth G. Demicco, Alexander J. Lazar, Dina Lev, and Ann Richmond

**Précis:** Results offer clinical implications for targeting the NF- $\kappa$ B/IL-6/STAT3 pathway to treat angiosarcoma, a rare but aggressive cancer of endothelial or lymph vessel cells that is poorly understood.

4696 **Ectopic ATP Synthase Blockade Suppresses Lung Adenocarcinoma Growth by Activating the Unfolded Protein Response**

Hsin-Yi Chang, Hsuan-Cheng Huang, Tsui-Chin Huang, Pan-Chyr Yang, Yi-Ching Wang, and Hsueh-Fen Juan

**Précis:** Findings elucidate a feature of mitochondrial ATP synthase expressed at the plasma membrane in lung cancer cells that might be exploited therapeutically.

4707 **MicroRNA-21 Modulates the Levels of Reactive Oxygen Species by Targeting SOD3 and TNF $\alpha$**

Xiangming Zhang, Wooi-Loon Ng, Ping Wang, LinLin Tian, Erica Werner, Huichen Wang, Paul Doetsch, and Ya Wang

**Précis:** An oncogenic microRNA thought to promote cancer mainly by affecting expression of growth regulatory genes may actually do so by regulating genes that promote reactive oxygen species formation, a root driver of carcinogenesis.

4714 **Truncated DNMT3B Isoform DNMT3B7 Suppresses Growth, Induces Differentiation, and Alters DNA Methylation in Human Neuroblastoma**

Kelly R. Ostler, Qiwei Yang, Timothy J. Looney, Li Zhang, Aparna Vasanthakumar, Yufeng Tian, Masha Kocherginsky, Stacey L. Raimondi, Jessica G. DeMaio, Helen R. Salwen, Song Gu, Alexandre Chlenski, Arlene Naranjo, Amy Gill, Radhika Peddinti, Bruce T. Lahn, Susan L. Cohn, and Lucy A. Godley

**Précis:** This study provides insights into the mechanistic basis for epigenetic changes in neuroblastoma, acting at the level of DNA methylation, with the potential to leverage treatments that use all-trans retinoic acid in this disease.

4724 **Unphosphorylated STAT1 Promotes Sarcoma Development through Repressing Expression of Fas and Bad and Conferring Apoptotic Resistance**

Mary A. Zimmerman, Nur-Taz Rahman, Dafeng Yang, Guy Lahat, Alexander J. Lazar, Raphael E. Pollock, Dina Lev, and Kebin Liu

**Précis:** Findings provide a molecular mechanism to explain the opposing functions between phosphorylated and unphosphorylated STAT1 in the control of the development of aggressive soft-tissue tumors.

## PREVENTION AND EPIDEMIOLOGY

4733 **Markers of B-Cell Activation in Relation to Risk of Non-Hodgkin Lymphoma**

Anneclaire J. De Roos, Dana K. Mirick, Kerstin L. Edlefsen, Andrea Z. LaCroix, Kenneth J. Kopecky, Margaret M. Madeleine, Larry Magpantay, and Otoniel Martínez-Maza

**Précis:** Evidence from a study of postmenopausal women suggests that B-cell activation plays a prominent role in the pathogenesis of non-Hodgkin lymphomas, pointing toward avenues for development of early diagnostic tests for this disease.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4744 **Hematologic  $\beta$ -Tubulin VI Isoform Exhibits Genetic Variability That Influences Paclitaxel Toxicity**

Luis J. Leandro-García, Susanna Leskelä, Lucía Inglada-Pérez, Iñigo Landa, Aguirre A. de Cubas, Agnieszka Maliszewska, Iñaki Comino-Méndez, Rocío Letón, Álvaro Gómez-Graña, Raúl Torres, Juan Carlos Ramírez, Sara Álvarez, José Rivera, Constantino Martínez, María Luisa Lozano, Alberto Cascón, Mercedes Robledo, and Cristina Rodríguez-Antona

**Précis:** A genetic variation found in a tubulin isoform expressed only in hematopoietic cells may explain the patient variation in myelosuppression that occurs after treatment with microtubule binding drugs.

4753 **Systemic Combination Virotherapy for Melanoma with Tumor Antigen-Expressing Vesicular Stomatitis Virus and Adoptive T-Cell Transfer**

Diana M. Rommelfanger, Phonphimon Wongthida, Rosa M. Diaz, Karen M. Kaluza, Jill M. Thompson, Timothy J. Kottke, and Richard G. Vile

**Précis:** Combining adoptive T-cell therapy with the immune stimulating benefits of oncolytic virotherapy might generate a truly systemic protocol for treatment of metastatic cancers without the need of direct access to the tumor.

- 4765 **B-Raf Activation Cooperates with PTEN Loss to Drive c-Myc Expression in Advanced Prostate Cancer**  
Jingqiang Wang, Takashi Kobayashi, Nicolas Floc'h, Carolyn Waugh Kinkade, Alvaro Aytes, David Dankort, Celine Lefebvre, Antonina Mitrofanova, Robert D. Cardiff, Martin McMahon, Andrea Califano, Michael M. Shen, and Cory Abate-Shen  
*Précis:* This study describing a novel model of advanced castration-resistant prostate cancers suggests a generalized approach to target Myc activation, a long-standing goal in cancer research, by combining inhibitors of the PI3K/Akt/mTOR and MAPK signaling pathways.
- 4777 **Effective Photothermal Chemotherapy Using Doxorubicin-Loaded Gold Nanospheres that Target EphB4 Receptors in Tumors**  
Jian You, Rui Zhang, Chiyi Xiong, Meng Zhong, Maritess Melancon, Sanjay Gupta, Alpa M. Nick, Anil K. Sood, and Chun Li  
*Précis:* A single nanodevice that targets tumor cells with both chemotherapy and phototherapy attacks is shown to exert a synergistic antitumor effect without increased toxicity in a preclinical mouse model.
- 4787 **Oxidation-Mediated DNA Cross-Linking Contributes to the Toxicity of 6-Thioguanine in Human Cells**  
Reto Brem and Peter Karran  
*Précis:* Two key contributors to the cytotoxicity of anticancer and immunosuppressant thiopurine drugs are their incorporation into DNA and their ability to increase levels of reactive oxygen species.
- 4796 **HER2 Overexpression Renders Human Breast Cancers Sensitive to PARP Inhibition Independently of Any Defect in Homologous Recombination DNA Repair**  
Somaira Newsheem, Tiffany Cooper, James A. Bonner, Albert F. LoBuglio, and Eddy S. Yang  
*Précis:* Findings may broaden clinical applications for PARP inhibitors in treating HER2<sup>+</sup> breast cancers, many of which ultimately become resistant to HER2 antibody therapies used widely in the clinic.
- 4818 **CCN6 Modulates BMP Signaling via the Smad-Independent TAK1/p38 Pathway, Acting to Suppress Metastasis of Breast Cancer**  
Anupama Pal, Wei Huang, Xin Li, Kathy A. Toy, Zaneta Nikolovska-Coleska, and Celina G. Kleer  
*Précis:* Findings identify a novel modifier pathway through which the extracellular matrix protein CCN6 limits the effects of the TGF- $\beta$  signaling axis on breast cancer invasion and metastasis.
- 4829 **PCA-1/ALKBH3 Contributes to Pancreatic Cancer by Supporting Apoptotic Resistance and Angiogenesis**  
Ichiro Yamato, Masayuki Sho, Keiji Shimada, Kiyohiko Hotta, Yuko Ueda, Satoshi Yasuda, Naoko Shigi, Noboru Konishi, Kazutake Tsujikawa, and Yoshiyuki Nakajima  
*Précis:* Findings suggest functional insights for a little-studied DNA repair gene in the pathophysiology of pancreatic cancer, with possible impacts on progression and therapeutic management.
- 4840 **TGF- $\beta$  and  $\alpha$ v $\beta$ 6 Integrin Act in a Common Pathway to Suppress Pancreatic Cancer Progression**  
Aram F. Hezel, Vikram Deshpande, Stephanie M. Zimmerman, Gianmarco Contino, Brinda Alagesan, Michael R. O'Dell, Lee B. Rivera, Jay Harper, Scott Lonning, Rolf A. Brekken, and Nabeel Bardeesy  
*Précis:* Findings from this preclinical study provide support for the argument that blocking the TGF- $\beta$  pathway may actually accelerate disease progression, challenging concepts about the potential benefit of such an approach in cancer patients.
- 4846 **The Antioxidant Tempol Reduces Carcinogenesis and Enhances Survival in Mice When Administered after Nonlethal Total Body Radiation**  
James B. Mitchell, Miriam R. Anver, Anastasia L. Sowers, Philip S. Rosenberg, Maria Figueroa, Angela Thetford, Murali C. Krishna, Paul S. Albert, and John A. Cook  
*Précis:* Findings prompt human studies of an antioxidant compound that can limit radiation-induced secondary malignancies after radiation therapy, and that may reduce the risks of cancer in individuals exposed to nonlethal radiation as a result of nuclear accidents or attacks.

## TUMOR AND STEM CELL BIOLOGY

- 4807 **Effective Combination Therapy for Malignant Glioma with TRAIL-Secreting Mesenchymal Stem Cells and Lipoxygenase Inhibitor MK886**  
Seong Muk Kim, Ji Sun Woo, Chang Hyun Jeong, Chung Heon Ryu, Jung Yeon Lim, and Sin-Soo Jeun  
*Précis:* Lipoxygenase inhibitors might be repositioned to help TRAIL-based cancer treatment strategies break through persistent translational impediments.

4856

**Candidate Pathways for Promoting Differentiation or Quiescence of Oligodendrocyte Progenitor-like Cells in Glioma**

Joseph D. Dougherty, Elena I. Fomchenko, Afua A. Akuffo, Eric Schmidt, Karim Y. Helmy, Elena Bazzoli, Cameron W. Brennan, Eric C. Holland, and Ana Milosevic

*Précis:* Translational profiling of mouse and human glioblastomas identified several candidate pathways that promote quiescence or differentiation rather than proliferation in these tumors, suggesting new therapeutic targets for combination treatment.

**CORRECTIONS**

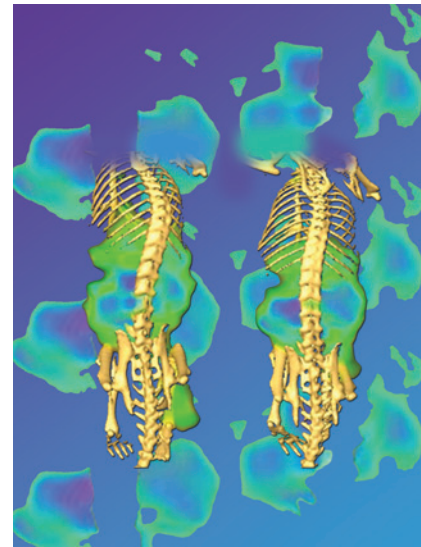
4869

**Correction: Deletion of the Endothelial Bmx Tyrosine Kinase Decreases Tumor Angiogenesis and Growth**

4870

**Correction: Prognostic PET <sup>18</sup>F-FDG Uptake Imaging Features Are Associated with Major Oncogenomic Alterations in Patients with Resected Non-Small Cell Lung Cancer****ABOUT THE COVER**

Complete tumor eradication by thermal ablation therapy alone is often difficult because of sub-lethal thermal dose in some areas of the tumor. For photothermal ablation therapy, it is highly desirable to selectively deliver combined thermal ablation therapy and other treatment modalities such as chemotherapy through a single nanodevice. Using doxorubicin-loaded hollow gold nanospheres conjugated with a high-affinity cyclic peptide recognizing EphB4 receptors, it was found that targeted nanoparticles displayed significantly higher tumor uptakes than nanoparticles without peptidyl homing ligands. Moreover, treatment with near-infrared laser led to synergistic antitumor effect without increased toxicities in a preclinical mouse model. For details, see article by You and colleagues on page 4777.



# Cancer Research

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

## 72 (18)

*Cancer Res* 2012;72:4609-4871.

**Updated version** Access the most recent version of this article at:  
<http://cancerres.aacrjournals.org/content/72/18>

**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/72/18>.  
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.