

# Contents

# Cancer Research

March 1, 2013 • Volume 73 • Number 5

## BREAKING ADVANCES

- 1447 | **Highlights from Recent Cancer Literature**

## REVIEW

- 1449 | **Everolimus in Advanced Pancreatic Neuroendocrine Tumors: The Clinical Experience**  
James C. Yao, Alexandria T. Phan, Valentine Jehl, Gaurav Shah, and Funda Meric-Bernstam

## PRIORITY REPORTS

- 1454 | **Chromothripsis and Focal Copy Number Alterations Determine Poor Outcome in Malignant Melanoma**  
Daniela Hirsch, Ralf Kemmerling, Sean Davis, Jordi Camps, Paul S. Meltzer, Thomas Ried, and Timo Gaiser  
*Précis:* Chromothripsis and focal copy number alterations determine poor outcome in patients with malignant melanoma, suggesting a role of chromothripsis as a genetic marker of aggressive cancer types.
- 1460 | **Cisplatin Hypersensitivity of Testicular Germ Cell Tumors Is Determined by High Constitutive Noxa Levels Mediated by Oct-4**  
Matthias Gutekunst, Thomas Mueller, Andrea Weilbacher, Michael A. Dengler, Jens Bedke, Stephan Kruck, Moshe Oren, Walter E. Aulitzky, and Heiko van der Kuip  
*Précis:* Important mechanistic findings offer an explanation for the long-standing question why testicular cancers are so susceptible to eradication with cisplatin treatment.

## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 1470 | **Multimodal Elucidation of Choline Metabolism in a Murine Glioma Model Using Magnetic Resonance Spectroscopy and <sup>11</sup>C-Choline Positron Emission Tomography**  
Hans F. Wehrli, Julian Schwab, Kathy Hasenbach, Gerald Reischl, Ghazaleh Tabatabai, Leticia Quintanilla-Martinez, Filip Jiru, Kamila Chughtai, Andras Kiss, Funda Cay, Daniel Bukala, Ron M.A. Heeren, Bernd J. Pichler, and Alexander W. Sauter  
*Précis:* Findings offer compelling evidence for complementary strengths of MRI and PET for noninvasive in vivo imaging of choline metabolism that is broadly important in cancer growth and progression.

- 1481 | **Acute and Fractionated Irradiation Differentially Modulate Glioma Stem Cell Division Kinetics**

Xuefeng Gao, J. Tyson McDonald, Lynn Hlatky, and Heiko Enderling

*Précis:* Different types of radiation treatment for aggressive brain tumors exert distinct effects on stem cells, with profound implications for treatment regimens used currently.

## MICROENVIRONMENT AND IMMUNOLOGY

- 1491 | **The Planar Cell Polarity Pathway Drives Pathogenesis of Chronic Lymphocytic Leukemia by the Regulation of B-Lymphocyte Migration**  
Markéta Kaucká, Karla Plevová, Šárka Pavlová, Pavlína Janovská, Archana Mishra, Jan Verner, Jiřina Procházková, Pavel Krejčí, Jana Kotašková, Petra Ovesná, Boris Tichý, Yvona Brychtová, Michael Doubek, Alois Kozubík, Jiří Mayer, Šárka Pospíšilová, and Vítězslav Bryja  
*Précis:* A class of molecules regulating cell polarity in circulating chronic lymphocytic leukemia cells mediates key pathogenic interactions with their microenvironment that determine prognosis.
- 1502 | **Autoantibody Signatures Involving Glycolysis and Spliceosome Proteins Precede a Diagnosis of Breast Cancer among Postmenopausal Women**  
Jon J. Ladd, Timothy Chao, Melissa M. Johnson, Ji Qiu, Alice Chin, Rebecca Israel, Sharon J. Pitteri, Jianning Mao, Mei Wu, Lynn M. Amon, Martin McIntosh, Christopher Li, Ross Prentice, Nora Disis, and Samir Hanash  
*Précis:* Circulating proteins, free autoantibodies, and protein-antibody complexes are defined in breast cancer patients, with possible implications for earlier detection of disease.
- 1514 | **Delicate Balance among Three Types of T Cells in Concurrent Regulation of Tumor Immunity**  
Liat Izhak, Elena Ambrosino, Shingo Kato, Stanley T. Parish, Jessica J. O'Konek, Hannah Weber, Zheng Xia, David Venzon, Jay A. Berzofsky, and Masaki Terabe  
*Précis:* Several distinct types of immune regulatory cells influence tumor immunity at the same time in a tumor, but their balance depends on T cells coordinately controlling them, possibly impacting immunotherapeutic strategies.

- 1524 **Acidity Generated by the Tumor Microenvironment Drives Local Invasion**  
Veronica Estrella, Tingan Chen, Mark Lloyd, Jonathan Wojtkowiak, Heather H. Cornnell, Arig Ibrahim-Hashim, Kate Bailey, Yoganand Balagurunathan, Jennifer M. Rothberg, Bonnie F. Sloane, Joseph Johnson, Robert A. Gatenby, and Robert J. Gillies  
*Précis:* Striking findings show that tumor invasion into adjacent normal tissues proceeds in the direction of low pH and that simply lowering the acidity of adjacent tissues in vivo by administering sodium bicarbonate is sufficient to block invasion.
- 1536 **Interstitial Flow in a 3D Microenvironment Increases Glioma Invasion by a CXCR4-Dependent Mechanism**  
Jennifer M. Munson, Ravi V. Bellamkonda, and Melody A. Swartz  
*Précis:* Strategies to alter interstitial flow patterns in brain tumors may combat invasive dissemination and therapeutic failures occurring in this disease.
- 1547 **Localized Immunotherapy via Liposome-Anchored Anti-CD137 + IL-2 Prevents Lethal Toxicity and Elicits Local and Systemic Antitumor Immunity**  
Brandon Kwong, S. Annie Gai, Jamal Elkhader, K. Dane Wittrup, and Darrell J. Irvine  
*Précis:* A nanoparticle-based platform for intratumoral delivery of potent immunotherapeutic agents enables antitumor immunity while avoiding systemic toxicities.
- 1570 **FoxA1 Specifies Unique Androgen and Glucocorticoid Receptor Binding Events in Prostate Cancer Cells**  
Biswajyoti Sahu, Marko Laakso, Päivi Pihlajamaa, Kristian Ovaska, Ievgenii Sinielnikov, Sampsa Hautaniemi, and Olli A. Jänne  
*Précis:* The findings of this study raise questions about the precise specificity of accepted androgen receptor pathways in castration-resistant prostate tumors under androgen-deprived states.
- 1581 **ALX1 Induces Snail Expression to Promote Epithelial-to-Mesenchymal Transition and Invasion of Ovarian Cancer Cells**  
Hong Yuan, Hiroaki Kajiyama, Satoko Ito, Nobuhisa Yoshikawa, Toshinori Hyodo, Eri Asano, Hitoki Hasegawa, Masao Maeda, Kiyofumi Shibata, Michinari Hamaguchi, Fumitaka Kikkawa, and Takeshi Senga  
*Précis:* A homeobox transcription factor implicated in mesenchymal differentiation and craniofacial development upregulates the EMT regulator Snail to drive invasion and metastasis.
- 1591 **Epigenetic Regulator Smc4 Functions as a Tumor Suppressor**  
Huei San Leong, Kelan Chen, Yifang Hu, Stanley Lee, Jason Corbin, Miha Pakusch, James M. Murphy, Ian J. Majewski, Gordon K. Smyth, Warren S. Alexander, Douglas J. Hilton, and Marnie E. Blewitt  
*Précis:* Results identify a chromatin modifier that may act through the same pathways as MLL chimeric proteins in driving a variety of hematopoietic cancers.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 1559 **Id-1 Is a Key Transcriptional Regulator of Glioblastoma Aggressiveness and a Novel Therapeutic Target**  
Liliana Soroceanu, Ryuichi Murase, Chandani Limbad, Eric Singer, Juanita Allison, Isabel Adrados, Rumi Kawamura, Arash Pakdel, Yayoi Fukuyo, Daniel Nguyen, Sabeena Khan, Robert Arauz, Garret L. Yount, Dan H. Moore, Pierre-Yves Desprez, and Sean D. McAllister  
*Précis:* A factor associated previously with angiogenesis support is found to control the aggressiveness and self-renewal potential of glioblastoma, the most common and deadly primary adult brain tumor.

## PREVENTION AND EPIDEMIOLOGY

- 1600 **Prospective Analysis of Body Mass Index, Physical Activity, and Colorectal Cancer Risk Associated with  $\beta$ -Catenin (CTNNB1) Status**  
Teppei Morikawa, Aya Kuchiba, Paul Lochhead, Reiko Nishihara, Mai Yamauchi, Yu Imamura, Xiaoyun Liao, Zhi Rong Qian, Kimmie Ng, Andrew T. Chan, Jeffrey A. Meyerhardt, Edward Giovannucci, Charles S. Fuchs, and Shuji Ogino  
*Précis:* Obesity and low physical activity associate with increased risk of colorectal cancers that do not involve  $\beta$ -catenin, the chief target of the WNT pathway, but not risk of  $\beta$ -catenin-positive colorectal cancers, which may be more aggressive.

---

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 1611 **Imatinib Radiosensitizes Bladder Cancer by Targeting Homologous Recombination**  
Boling Qiao, Martin Kerr, Blaz Groselj, Mark T.W. Teo, Margaret A. Knowles, Robert G. Bristow, Roger M. Phillips, and Anne E. Kiltie  
*Précis:* The tyrosine kinase inhibitor Gleevec may have additional uses to radiosensitize tumors that are defective in non-homologous end joining (NHEJ), with the potential to greatly expand clinical applications of this agent.
- 1621 **Targeting XRCC1 Deficiency in Breast Cancer for Personalized Therapy**  
Rebeka Sultana, Tarek Abdel-Fatah, Rachel Abbotts, Claire Hawkes, Nada Albarakati, Claire Seedhouse, Graham Ball, Stephen Chan, Emad A. Rakha, Ian O. Ellis, and Srinivasan Madhusudan  
*Précis:* Findings suggest how XRCC1 deficiency in breast cancer can inform choice of targeted chemotherapies for treatment, based on the synthetic lethality that can be achieved with the inhibition of particular mechanisms of DNA double-strand break repair.

## TUMOR AND STEM CELL BIOLOGY

- 1635 **HER2 Drives Luminal Breast Cancer Stem Cells in the Absence of HER2 Amplification: Implications for Efficacy of Adjuvant Trastuzumab**  
Suthinee Ithimakin, Kathleen C. Day, Fayaz Malik, Qin Zen, Scott J. Dawsey, Tom F. Bersano-Begey, Ahmed A. Quraishi, Kathleen Woods Ignatoski, Stephanie Daignault, April Davis, Christopher L. Hall, Nallasivam Palanisamy, Amber N. Heath, Nader Tawakkol, Tahra K. Luther, Shawn G. Clouthier, Whitney A. Chadwick, Mark L. Day, Celina G. Kleer, Dafydd G. Thomas, Daniel F. Hayes, Hasan Korkaya, and Max S. Wicha  
*Précis:* HER2 selectively regulates the cancer stem cell population in luminal breast cancers, perhaps explaining the clinical benefits of adjuvant trastuzumab therapy in tumors where the HER2 gene is not amplified.

---

## ABOUT THE COVER

Intravital image of tumor growth within a dorsal window chamber. HCT116/GFP-expressing tumors were grown within a dorsal window chamber, where its growth was monitored over time. Images were captured following excitation with an Argon laser at 488 nm and emission was collected with a 498–538 nm bandpass filter using an Olympus FV1000 multiphoton microscope. Tumor at day 14 was pseudo-colored red in order to superimpose the tumor image on day 4 (green). Growth was quantified along radial lines from the centroid of the day 4 tumor and compared with registered images of the peritumoral pH to correlate growth and invasion to acidity. For details, see article by Estrella and colleagues on page 1524.

