**Contents**

**Cancer Research**
August 15, 2013 • Volume 73 • Number 16

**BREAKING ADVANCES**

4963  Highlights from Recent Cancer Literature

**REVIEWS**

4965  Targeting the Tumor Microenvironment: From Understanding Pathways to Effective Clinical Trials
Hua Fang and Yves A. DeClerck

4978  p63 Sharp1, and HIFs: Master Regulators of Metastasis in Triple-Negative Breast Cancer
Stefano Piccolo, Elena Enzo, and Marco Montagner

**PERSPECTIVE**

4982  Early B-Cell Differentiation in Merkel Cell Carcinomas: Clues to Cellular Ancestry
Axel zur Hausen, Dorit Rennspiess, Veronique Winnepenninckx, Ernst-Jan Speel, and Anna Kordelia Kurz

**MEETING REPORT**

4988  The 19th Annual Prostate Cancer Foundation Scientific Retreat: Meeting Report
Guneet Walia, Kenneth J. Pienta, Jonathan W. Simons, and Howard R. Soule

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

4992  Metabolic Characterization of Hepatocellular Carcinoma Using Nontargeted Tissue Metabolomics
Qiang Huang, Yexiong Tan, Peiyuan Yin, Guozhu Ye, Peng Gao, Xin Lu, Hongyang Wang, and Guowang Xu

**MICROENVIRONMENT AND IMMUNOLOGY**

5003  Myeloid-DerivedSuppressor Cells as a Vehicle for Tumor-Specific Oncolytic Viral Therapy
Samuel Eisenstein, Brian A. Coxley, Karen Briley-Saebo, Ge Ma, Hui-ming Chen, Marcia Meseck, Stephen Ward, Celia Divino, Savio Woo, Shu-Hsia Chen, and Ping-Ying Pan

**PÉcise:** This preclinical study highlights the efficacy of a specific myeloid cell type to serve as a key delivery vehicle for oncolytic viruses that significantly improves tumor killing, prolonging survival and minimizing toxicity.

5016  TGF-β Modulates Ovarian Cancer Invasion by Upregulating CAF-Derived Versican in the Tumor Microenvironment
Tsz-Lun Yeung, Cecilia S. Leung, Kwong-Kwok Wong, Goli Samimi, Melissa S. Thompson, Jinsong Liu, Tarrik M. Zaid, Sue Ghosh, Michael J. Birrer, and Samuel C. Mok

**PÉcise:** These findings suggest a central mechanism through which TGF-β-targeted therapies may alter the invasive capacity of cancer cells by acting through their microenvironment.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

5029  Gene Profiling of Canine B-Cell Lymphoma Reveals Germinal Center and Postgerminal Center Subtypes with Different Survival Times, Modeling Human DLBCL
Kristy L. Richards, Alison A. Motsinger-Reif, Hsiao-Wei Chen, Yuri Fedoriw, Cheng Fan, Dahlia M. Nielsen, George W. Small, Rachael Thomas, Chris Smith, Sanjeev S. Dave, Charles M. Perou, Matthew Breen, Luke B. Borst, and Steven E. Suter

**PÉcise:** This study reveals the remarkable molecular similarity between human and canine forms of a certain type of B-cell lymphoma, overcoming limitations in existing models that have impeded the advancement of etiologic and therapeutic insights.
Extracellular RNA Liberates Tumor Necrosis Factor-α to Promote Tumor Cell Trafficking and Progression

Silvia Fischer, Sabine Gesterich, Barbara Griemert, Anne Schänzer, Till Acker, Hellmut G. Augustin, Anna-Karin Olsson, and Klaus T. Preisner

Precis: These findings establish crucial functions for extracellular RNA released from tumor cells in driving invasion and progression, and suggest in vivo applications for RNase1 as a provocative therapeutic approach.

Extracellular RNA Liberates Tumor Necrosis Factor-α to Promote Tumor Cell Trafficking and Progression

Silvia Fischer, Sabine Gesterich, Barbara Griemert, Anne Schänzer, Till Acker, Hellmut G. Augustin, Anna-Karin Olsson, and Klaus T. Preisner

Precis: These findings establish crucial functions for extracellular RNA released from tumor cells in driving invasion and progression, and suggest in vivo applications for RNase1 as a provocative therapeutic approach.

Critical Tumor Suppressor Function Mediated by Epithelial Mig-6 in Endometrial Cancer

Tae Hoon Kim, Dong-Kee Lee, Sung-Nam Cho, Grant D. Orvis, Richard R. Behringer, John P. Lydon, Bon Jeong Ku, Adrienne S. McCampbell, Russell R. Broaddus, and Jae-Wook Jeong

Precis: This study provides insights into how progesterone prevents endometrial cancer, a longstanding question for which mechanistic knowledge might advance thinking about how to use this hormone in treatment.

Acquired Expression of NFATc1 Downregulates E-Cadherin and Promotes Cancer Cell Invasion

Tsukasa Oikawa, Atsuko Nakamura, Nobuyuki Onishi, Taketo Yamada, Koichi Matsuo, and Hideyuki Saya

Precis: Carcinoma cells that switch on expression of an important hematopoietic transcription factor acquire new capacities for invasive movement and growth.

14-3-3 Proteins Modulate the ETS Transcription Factor ETVI in Prostate Cancer

Sangphil Oh, Sook Shin, Stan A. Lightfoot, and Ralf Janknecht

Precis: This article provides mechanistic insight into the pathophysiology of multiple tumors, including prostate cancer and melanomas.

The DREAM Complex Mediates GIST Cell Quiescence and Is a Novel Therapeutic Target to Enhance Imatinib-Induced Apoptosis

Sergei Boichuk, Joshua A. Parry, Kathleen R. Makiebski, Larisa Litovchick, Julianne L. Baron, James P. Zewe, Agnieszka Wozniak, Keith R. Mehalek, Nina Korzeniewski, Danushka S. Seneviratne, Patrick Schoëfis, Maria Debiec-Rychter, James A. DeCaprio, and Anette Duensing

Precis: Dissecting the molecular pathways that lead to tumor cell quiescence after targeted therapies leads to novel treatment strategies that potentially can extend survival.

Reprogramming the Chromatin Landscape: Interplay of the Estrogen and Glucocorticoid Receptors at the Genomic Level

Tina B. Miranda, Ty C. Yoss, Myong-Hee Sung, Songjoon Baek, Sam John, Mary Hawkins, Lars Granntved, R. Louis Schiltz, and Gordon L. Hager

Precis: These results define an epigenetic mechanism that can explain how the estrogen and glucocorticoid receptors can dictate the binding patterns of other steroid receptors across the genome.
RHPN2 Drives Mesenchymal Transformation in Malignant Glioma by Triggering RhoA Activation

Carla Danussi, Uri David Akavia, Francesco Niola, Andreja Jovic, Anna Lasorella, Dana Pe’er, and Antonio Iavarone

Précis: These results identify a key genetic module promoting the most aggressive cancer phenotype in glioblastoma patients, leading to the worst outcomes.

Prevention and Epidemiology

A Sequence Polymorphism in miR-608 Predicts Recurrence after Radiotherapy for Nasopharyngeal Carcinoma

Jian Zheng, Jieqiong Deng, Mang Xiao, Lei Yang, Liyuan Zhang, Yonghe You, Min Hu, Na Li, Hongchun Wu, Wei Li, Jiachun Lu, and Yifeng Zhou

Précis: A single-nucleotide polymorphism in a microRNA that affects chromatid break repair can predict clinical outcomes after radiotherapy in nasopharyngeal cancer, with potentially broader implications for other DNA damaging cancer therapies.

Gleason Grade Progression Is Uncommon


Précis: These findings suggest that prostate tumor grade may be established early in tumorigenesis, with one implication being that patients newly diagnosed with early-stage and lower-grade disease may feel more comfortable on an active surveillance protocol.

Therapeutics, Targets, and Chemical Biology

A Novel Class of Anticancer Compounds Targets the Actin Cytoskeleton in Tumor Cells


Précis: This study offers a preclinical proof of concept for small molecules that target the actin cytoskeleton of cancer cells as an efficacious treatment strategy.

mTOR Signaling Feedback Modulates Mammary Epithelial Differentiation and Restrains Invasion Downstream of PTEN Loss

Susmita Ghosh, Lidensy Varela, Akshay Sood, Ben Ho Park, and Tamara L. Lotan

Précis: This report suggests additional new cautions regarding the use of mTOR inhibitors for cancer treatment, contributing to ongoing controversies about their potential utility.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Abstract</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5232</td>
<td>Manganoporphyrins Increase Ascorbate-Induced Cytotoxicity by Enhancing H₂O₂ Generation</td>
<td>Malvika Rawal, Samuel R. Schroeder, Brett A. Wagner, Cameron M. Cushing, Jessemae L. Welsh, Anna M. Button, Juan Du, Zita A. Sibenaller, Garry R. Buettner, and Joseph J. Cullen</td>
<td>Précis: A class of porphyrins being developed as superoxide dismutase mimics have the potential to safely leverage the anticancer effects of pharmacologic ascorbate therapy.</td>
<td>5266</td>
</tr>
<tr>
<td>5242</td>
<td>Intratumoral Modeling of Gefitinib Pharmacokinetics and Pharmacodynamics in an Orthotopic Mouse Model of Glioblastoma</td>
<td>Jyoti Sharma, Hua Lv, and James M. Gallo</td>
<td>Précis: The major issue of heterogeneity in solid tumors, having been characterized yet again by deep sequencing studies, dramatically affects intratumoral drug activities, for which better models are needed to enhance our understanding.</td>
<td>5277</td>
</tr>
<tr>
<td>5253</td>
<td>Potassium Channel KCNA1 Modulates Oncogene-Induced Senescence and Transformation</td>
<td>Hélène Lallet-Daher, Clotilde Wiel, Delphine Gitenay, Naveen Navaratnam, Arnaud Augert, Benjamin Le Calvé, Stéphanie Verbeke, David Carling, Sébastien Aubert, David Vindrieux, and David Bernard</td>
<td>Précis: This study identifies a novel tumor suppressor pathway that restricts oncogenesis by triggering premature senescence.</td>
<td>5288</td>
</tr>
<tr>
<td>5266</td>
<td>CTEN Prolongs Signaling by EGFR through Reducing Its Ligand-Induced Degradation</td>
<td>Shiao-Ya Hong, Yi-Ping Shih, Tianhong Li, Kermit L. Carraway III, and Su Hao Lo</td>
<td>Précis: The most effective therapeutic targeting of EGFR for cancer therapy will likely be based in part on an understanding of the epigenetic conditions that contribute to its effective stabilization.</td>
<td>5277</td>
</tr>
<tr>
<td>5277</td>
<td>O-GlcNAc Transferase Integrates Metabolic Pathways to Regulate the Stability of c-MYC in Human Prostate Cancer Cells</td>
<td>Harri M. Itkonen, Sarah Minner, Ingrid J. Guldvik, Mareike Julia Sandmann, Maria Christina Tsourlakis, Viktor Berge, Aud Svindland, Thorsten Schollm, and Ian G. Mills</td>
<td>Précis: Targeting a protein glycosylation pathway that is dysregulated by metabolic flux in cancer cells blocks MYC and inhibits cancer cell proliferation, possibly offering a broad-based anticancer strategy.</td>
<td>5288</td>
</tr>
<tr>
<td>5288</td>
<td>JAK-STAT Blockade Inhibits Tumor Initiation and Clonogenic Recovery of Prostate Cancer Stem-like Cells</td>
<td>Paula Kroon, Paul A. Berry, Michael J. Stower, Greta Rodrigues, Vincent M. Mann, Matthew Simms, Deepak Bhaisin, Somsundaran Chettiar, Chenglong Li, Pui-Kai Li, Norman J. Maitland, and Anne T. Collins</td>
<td>Précis: The most primitive cells in prostate cancer require STAT3 for survival, further rationalizing this molecule as a therapeutic target to treat advanced prostate cancer.</td>
<td></td>
</tr>
</tbody>
</table>
ABOUT THE COVER

The actin cytoskeleton, due to its role in many processes involved in cellular transformation, has long been a sought after anticancer target, yet attempts to develop such compounds have been hampered by unacceptable toxicity. By targeting the other core polymer system of the microfilaments, tropomyosin, it is possible to discriminate between actin filaments required for sarcomeric function and those required for tumor growth. In silico modeling shows the predicted association of the first in class antitropomyosin compound, TR100, with the C-terminus of a cancer-associated tropomyosin, Tm5NM1. The interaction between Tm5NM1 and TR100 results in disruption of actin filament organization and death of tumor cells, both in vitro and in vivo. For details, see article by Stehn and colleagues on page 5169.