Contents

BREAKING ADVANCES

3191 Highlights from Recent Cancer Literature

REVIEWS

3193 The MET Oncogene in Glioblastoma Stem Cells: Implications as a Diagnostic Marker and a Therapeutic Target
Carla Boccaccio and Paolo M. Comoglio

3200 Vesicle Trafficking and RNA Transfer Add Complexity and Connectivity to Cell–Cell Communication
Charles T. Roberts Jr and Peter Kurre

INTEGRATED SYSTEMS AND TECHNOLOGIES

3206 Application of Raman Spectroscopy to Identify Microcalcifications and Underlying Breast Lesions at Stereotactic Core Needle Biopsy
Ishan Barman, Narahara Chari Dingari, Anushree Saha, Sasha McGee, Luis H. Galindo, Wendy Liu, Donna Plecha, Nina Klein, Ramachandra Rao Dasari, and Maryann Fitzmaurice

3208 Manganese-Enhanced MRI Reveals Early-Phase Radiation-Induced Cell Alterations In Vivo
Shigeyoshi Saito, Sumitaka Hasegawa, Aiko Sekita, Rumiana Bakalova, Takako Furukawa, Kenya Murase, Tsumeo Saga, and Ichio Aoki

MICROENVIRONMENT AND IMMUNOLOGY

3225 The Endogenous Tryptophan Metabolite and NAD⁺ Precursor Quinolinic Acid Confers Resistance of Gliomas to Oxidative Stress
Felix Sahm, Iris Oezen, Christiane A. Opitz, Bernhard Radl shimmer, Andreas von Deimling, Tilman Ahrendt, Seray Adams, Helge B. Bode, Gilles J. Guillemín, Wolfgang Wick, and Michael Platten

MOLECULAR AND CELLULAR PATHOBIOLOGY

3235 Hypoxia Triggers Hedgehog-Mediated Tumor–Stromal Interactions in Pancreatic Cancer

3248 Single Copies of Mutant KRAS and Mutant PIK3CA Cooperate in Immortalized Human Epithelial Cells to Induce Tumor Formation

Precis: These findings provide evidence for a novel molecular mechanism that explains the high levels of hypoxia and desmoplasia that contribute to therapy resistance in pancreatic cancer.

Precis: This study reports a noninvasive method to monitor cell-cycle alterations in tumors based on manganese uptake and MRI offering a potentially useful tool for longitudinal studies to optimize radiotherapy.
Inhibition of Tumor Cell Migration by LD22-4, an N-Terminal Fragment of 24-kDa FGFR2, Is Mediated by Neuropilin 1
Ling Zhang, Graham C. Parry, and Eugene G. Levin

Précis: Definition of a cell surface receptor for an inhibitor of cancer cell migration suggests a novel approach to tumor suppression.

DNA Methylation-Mediated Repression of miR-886-3p Predicts Poor Outcome of Human Small Cell Lung Cancer
Jianzhong Cao, Yongmei Song, Nan Bi, Jie Shen, Wenyang Liu, Jing Fan, Guogui Sun, Tong Tong, Jie He, Yuankai Shi, Xun Zhang, Ning Lu, Yinghua He, Hongyu Zhang, Kelong Ma, Xiaoying Luo, Lei Lx, Hui Deng, Jing Cheng, Jingde Zhu, Luhua Wang, and Qimin Zhan

Précis: These findings identify a little-studied microRNA the epigenetic downregulation of which strongly affects clinical outcomes and malignant cell behaviors in small-cell lung cancer.

PFI-1, a Highly Selective Protein Interaction Inhibitor, Targeting BET Bromodomains
Sarah Picard, David Da Costa, Angeliki Thanasopoulou, Panagis Filippakopoulos, Paul V. Fish, Martin Philpott, Oleg Fedorov, Paul Brennan, Mark E. Bunnage, Dafydd R. Owen, James E. Bradner, Philippe Taniere, Brendan O’Sullivan, Susanne M. Muller, Juerg Schwaller, Tatjana Stankovic, and Stefan Knapp

Précis: This study suggests that it may be possible to target an important transcriptional regulatory domain that has been implicated in a broad number of aggressive blood cancers, as a generalizable therapeutic approach.

Bevacizumab-Induced Normalization of Blood Vessels in Tumors Hampers Antibody Uptake
Marlous Arjaans, Thijs H. Oude Munnik, Sjouke F. Oosting, Anton G.T. Terwisscha van Scheltinga, Jourik A. Gietema, Erik T. Garbacik, Martin Philpott, Oleg Fedorov, Paul Brennan, Mark E. Bunnage, Dafydd R. Owen, Eugene G. Levin

Précis: Bevacizumab treatment decreases tumor uptake of antibodies by vessel normalization, and this should be taken into account in the design of clinical trials that combine bevacizumab with other antibodies.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3356</td>
<td>Threshold Levels of ABL Tyrosine Kinase Inhibitors Retained in Chronic Myeloid Leukemia Cells Determine Their Commitment to Apoptosis</td>
<td>Thomas O'Hare, Christopher A. Eide, Anupriya Agarwal, Lauren T. Adrian, Matthew S. Zabriskie, Ryan J. MacKenzie, Dorian H. LaTocha, Kara J. Johnson, Huihong You, Jenny Luo, Steven M. Riddle, Bryan D. Marks, Kurt W. Vogel, Dennis R. Koop, John Appgar, Jeffrey W. Tyner, Michael W. Deininger, and Brian J. Drucker</td>
</tr>
<tr>
<td>3371</td>
<td>Simultaneous Targeting of Tumor Antigens and the Tumor Vasculature Using T Lymphocyte Transfer Synergize to Induce Regression of Established Tumors in Mice</td>
<td>Dhanalakshmi Chinnasamy, Eric Tran, Zhiya Yu, Richard A. Morgan, Nicholas P. Restifo, and Steven A. Rosenberg</td>
</tr>
<tr>
<td>3393</td>
<td>Regulation of FANCD2 by the mTOR Pathway Contributes to the Resistance of Cancer Cells to DNA Double-Strand Breaks</td>
<td>Changxian Shen, Duane Oswald, Doris Phelp, Hakam Cam, Christopher E. Pellek, Qishen Pang, and Peter J. Houghton</td>
</tr>
<tr>
<td>3402</td>
<td>Elevation of Receptor Tyrosine Kinases by Small Molecule AKT Inhibitors in Prostate Cancer Is Mediated by Pim-1</td>
<td>Bo Cen, Sandeep Mahajan, Wexnue Wang, and Andrew S. Kraft</td>
</tr>
<tr>
<td>3412</td>
<td>CIP4 Controls CCL19-Driven Cell Steering and Chemotaxis in Chronic Lymphocytic Leukemia</td>
<td>Gema Malet-Engra, Julien Vaud, Loïc Ysebaert, Manon Farcé, Fanny Lafouresse, Guy Laurent, Frédérique Gaits-Iacovoni, Giorgio Scita, and Loïc Dupré</td>
</tr>
<tr>
<td>3425</td>
<td>miR145 Targets the SOX9/ADAM17 Axis to Inhibit Tumor-Initiating Cells and IL-6–Mediated Paracrine Effects in Head and Neck Cancer</td>
<td>Cheng-Chia Yu, Lo-Lin Tsai, Mong-Lien Wang, Chuan-Hang Yu, Wen-Liang Lo, Yun-Ching Chang, Guang-Yuh Chiu, Ming-Tung Chou, and Shih-Hwa Chou</td>
</tr>
<tr>
<td>3441</td>
<td>Cytomegalovirus Contributes to Glioblastoma in the Context of Tumor Suppressor Mutations</td>
<td>Richard L. Price, Jeun Song, Katherine Bingmer, Tae Hyong Kim, Ji-Youn Yi, Michal O. Nowicki, Xiaokui Mo, Todd Hollon, Eric Murman, Christopher Alvarez-Breckenridge, Soledad Fernandez, Balveen Kaur, Andreana Rivera, Michael Oglesbee, Charles Cook, E. Antonio Chiocca, and Chang-Hyuk Kwon</td>
</tr>
<tr>
<td>3451</td>
<td>Notch3 Functions as a Tumor Suppressor by Controlling Cellular Senescence</td>
<td>Hang Cui, Yahui Kong, Mei Xu, and Hong Zhang</td>
</tr>
</tbody>
</table>

**TUMOR AND STEM CELL BIOLOGY**

This study offers proof of principle for using antiangiogenic drugs to enhance the efficacy of adoptive T-cell therapies for cancer treatment.

This study offers important new mechanistic insights into how leukemia cells migrate, with potentially important implications for understanding how to block invasive growth by these cells.

This study provides the basis for the sensitization of cancer cells to DNA damaging agents by targeting the mTOR pathway and gives insight into potential strategies that may enhance therapeutic activity or reduce sequelae from high-dose therapies, particularly in children.
Dual Role of the Antioxidant Enzyme Peroxiredoxin 6 in Skin Carcinogenesis
Frank Rolfs, Marcel Huber, Florian Gruber, Friederike Böhm, Herbert J. Pfister, Valery N. Bochkov, Erwin Tschachler, Reinhard Dummer, Daniel Hohl, Matthias Schäfer, and Sabine Werner

Précis: Antioxidant functions do not contribute exclusively to tumor suppression, as widely believed, but can also promote tumor development depending on the stage of the disease.

Growth of Triple-Negative Breast Cancer Cells Relies upon Coordinate Autocrine Expression of the Proinflammatory Cytokines IL-6 and IL-8

Précis: Findings offer a preclinical proof of principle to improve therapy of triple-negative breast cancer, a particularly aggressive disease subtype lacking effective mechanism-based interventions.

ABOUT THE COVER
In gliomas, constitutive metabolism of the essential amino acid tryptophan leads to the accumulation of the tryptophan metabolite quinolinic acid. Quinolinic acid is used by tumor cells to generate NAD⁺, thus contributing to the resistance towards radiotherapy and chemotherapy by replenishing depleted intracellular NAD pools. Using Western blot analyses and immunohistochemistry, it was found that the key enzyme leading to accumulation of quinolinic acid, 3-hydroxyanthranilate oxygenate (3-HAO), is expressed by tumor-infiltrating monocytes. Thus, infiltrating monocytes contribute to resistance to cytotoxic therapies in malignant gliomas. For details, see article by Sahm and colleagues on page 3225.