BREAKING ADVANCES

2927 Highlights from Recent Cancer Literature

REVIEWS

2929 AMPK: A Contextual Oncogene or Tumor Suppressor?
Jiyong Liang and Gordon B. Mills

2936 KDM4/JMJD2 Histone Demethylases: Epigenetic Regulators in Cancer Cells
William L. Berry and Ralf Janknecht

PERSPECTIVES

2943 Vascular Normalization as an Emerging Strategy to Enhance Cancer Immunotherapy
Yuhui Huang, Shom Goel, Dan G. Duda, Dai Fukumura, and Rakesh K. Jain

MEETING REPORT

2949 Center of Cancer Systems Biology Second Annual Workshop—Tumor Metronomics: Timing and Dose Level Dynamics
Philip Hahnfeldt, Lynn Hlatky, and Giannoula Lakka Klement

CLINICAL STUDIES

2955 Elevated ALCAM Shedding in Colorectal Cancer Correlates with Poor Patient Outcome

Precis: This study illustrates how monitoring the biological activity of a factor rather than its expression in cancer patients can provide a more informative metric to predict malignant progression.

INTEGRATED SYSTEMS AND TECHNOLOGIES

2965 Complex Tumor Genomes Inferred from Single Circulating Tumor Cells by Array-CGH and Next-Generation Sequencing
Ellen Heitzer, Martina Auer, Christin Gasch, Martin Fichler, Peter Ulz, Eva Maria Hoffmann, Sigurd Lax, Julie Waldiquel-Geigl, Oliver Mauermann, Carolin Lackner, Gerald Höfler, Florian Eissner, Heinz Sill, Hellmut Samonigg, Klaus Pantel, Sabine Riethdorf, Thomas Bauernhofer, Jochen B. Geigl, and Michael R. Speicher

Precis: This study paves the way to use circulating tumor cells as a liquid biopsy in cancer patients, providing more effective options to monitor tumor genomes that are prone to change during progression, treatment, and relapse.

2976 Response Classification Based on a Minimal Model of Glioblastoma Growth Is Prognostic for Clinical Outcomes and Distinguishes Progression from Pseudoprogression
Maxwell Lewis Neal, Andrew D. Trister, Sunyoung Ahn, Anne Baldock, Carly A. Bridge, Laura Guyman, Jordan Lange, Rita Sodt, Tyler Cloke, Albert Lai, Timothy F. Cloughesy, Maciej M. Mrugala, Jason K. Rockhill, Russell C. Rockne, and Kristin R. Swanson

Precis: Results describe a novel and simple method to measure the effectiveness of glioblastoma therapies during periods of treatment when timely adjustments may be made to improve patient outcomes.

MICROENVIRONMENT AND IMMUNOLOGY

2987 Vaccination for Invasive Canine Meningioma Induces In Situ Production of Antibodies Capable of Antibody-Dependent Cell-Mediated Cytotoxicity

Precis: Canine models for certain types of CNS malignancy appear to offer superior features for preclinical exploration and evaluation of new therapies, such as the one reported in this study.
### MOLECULAR AND CELLULAR PATHOBIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Contributors</th>
<th>précis</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2998</td>
<td>Adipocytes Cause Leukemia Cell Resistance to L-Asparaginase via Release of Glutamine</td>
<td>Ehsan A. Ehsanipour, Xia Sheng, James W. Behan, Xingchao Wang, Anna Butturini, Vassilios I. Avramis, and Steven D. Mittelman</td>
<td>Studies identify mechanisms behind the poor survival of obese leukemia patients through impaired asparaginase response.</td>
<td>3041</td>
</tr>
<tr>
<td>3007</td>
<td>Pancreatic Cancer-Associated Stellate Cells Promote Differentiation of Myeloid-Derived Suppressor Cells in a STAT3-Dependent Manner</td>
<td>Thomas A. Mace, Zeenath Ameen, Amy Collins, Sylvia Wojcik, Markus Mair, Gregory S. Young, James R. Fuchs, Tim D. Eubank, Wendy L. Frankel, Tanios Bekai-Saab, Mark Bloomston, and Gregory B. Lesinski</td>
<td>A well-known stromal cell population found in pancreatic tumors is found to secrete soluble factors that convert myeloid cells to an immunosuppressive phenotype that promotes tumoral immune escape and progression.</td>
<td>3051</td>
</tr>
<tr>
<td>3019</td>
<td>Inhibition of Histone Demethylase JMJD1A Improves Anti-Angiogenic Therapy and Reduces Tumor-Associated Macrophages</td>
<td>Tsuyoshi Osawa, Rika Tsuchida, Masashi Muramatsu, Teppei Shimamura, Feng Wang, Jun-ichi Suehiro, Yasuharu Kanki, Youichi Wada, Yasuhiro Yuasa, Hiroyuki Aburatani, Satoru Miyano, Takashi Minami, Tatsuhiko Kodama, and Masahumi Shibuya</td>
<td>Findings highlight a strategy to target cancer cells resistant to hypoxia and nutrient starvation as an approach to heighten sensitivity to antiangiogenic drugs and to reduce risks of drug resistance and tumor recurrence.</td>
<td>3062</td>
</tr>
<tr>
<td>3029</td>
<td>Cowden Syndrome-Related Mutations in PTEN Associate with Enhanced Proteasome Activity</td>
<td>Xin He, Nicholas Arrotta, Deepa Radhakrishnan, Yu Wang, Todd Romigh, and Charis Eng</td>
<td>The results of this study may help resolve the loose genotype-phenotype correlations that occur in a spectrum of clinical syndromes, marked by germline PTEN mutations, by tracing their common effects to alterations in proteasome activity that are affected both by PTEN protein stability and subcellular localization.</td>
<td>3075</td>
</tr>
</tbody>
</table>

### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Contributors</th>
<th>précis</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3041</td>
<td>Oncogenic NRAS, Required for Pathogenesis of Embryonic Rhabdomyosarcoma, Relies upon the HMGAA2–IGF2BP2 Pathway</td>
<td>Zhizhong Li, Yunyu Zhang, Krishnan Ramanujan, Yan Ma, David G. Kirsch, and David J. Glass</td>
<td>Findings identify the upstream elements controlling a core oncogenic driver in embryonic rhabdomyosarcomas, suggesting novel points to target therapeutic inventions against this aggressive pediatric tumor.</td>
<td>3051</td>
</tr>
<tr>
<td>3051</td>
<td>Acquired Resistance to EGFR Inhibitors Is Associated with a Manifestation of Stem Cell–like Properties in Cancer Cells</td>
<td>Kazuhiko Shien, Shinichi Toyooka, Hiromasa Yamamoto, Junichi Soh, Masaru Jida, Kelsie L. Thu, Shinsuke Hashida, Yuho Maki, Eiki Ichihara, Hiroaki Asano, Kazunori Tsukuda, Nagio Takigawa, Katsuyuki Kiura, Adi F. Gazdar, Wan L. Lam, and Shinichiro Miyoshi</td>
<td>In lung cancer, malignant cells with stem cell-like properties appeared as acquired resistance emerged to EGFR inhibitors, reinforcing concerns that while such treatments may be effective initially, they may also promote progression at later times.</td>
<td>3062</td>
</tr>
<tr>
<td>3062</td>
<td>Novel HSP90 Inhibitor NVP-HSP990 Targets Cell-Cycle Regulators to Ablate Olig2-Positive Glia Tumor–Initiating Cells</td>
<td>Jun Fu, Dimpy Koul, Jun Yao, Shuzhen Wang, Ying Yuan, Howard Colman, Erik. P. Sulman, Frederick. F. Lang, and W.K. Alfred Yung</td>
<td>Findings suggest that HSP90 inhibitors being evaluated in clinical trials may be efficacious against deadly brain tumors that express a particular type of cancer stem-like cell.</td>
<td>3075</td>
</tr>
<tr>
<td>3075</td>
<td>Efficacy and Mechanism-of-Action of a Novel Superagonist Interleukin-15: Interleukin-15 Receptor αSu/Fc Fusion Complex in Syngeneic Murine Models of Multiple Myeloma</td>
<td>Wenzin Xu, Monica Jones, Bai Liu, Xiaoyun Zhu, Christopher B. Johnson, Ana C. Edwards, Lin Kong, Emily K. Jeng, Kaiping Han, Warren D. Marcus, Mark P. Rubinstein, Peter R. Rhode, and Hing C. Wong</td>
<td>Findings offer preclinical proof-of-concept for an engineered T-cell stimulant that mediates antitumor activity against multiple myeloma, rationalizing its clinical evaluation.</td>
<td></td>
</tr>
</tbody>
</table>
Cytotoxic Activity of Tivantinib (ARQ 197) Is Not Due Solely to c-MET Inhibition
Ryohei Katayama, Aki Aoyama, Takao Yamori, Jie Qi, Tomoko Oh-hara, Youngchul Song, Jeffrey A. Engelman, and Naoya Fujita

Précis: This study finds that a drug in clinical trials exerts its antitumor activity by blocking tubulin polymerization as well as c-Met activity.

RXRa Inhibits the NRF2-ARE Signaling Pathway through a Direct Interaction with the Neh7 Domain of NRF2
Hongyan Wang, Kaihua Liu, Miao Geng, Peng Gao, Xiaoyuan Wu, Yan Hai, Yangxia Li, Yulong Li, Lin Luo, John D. Hayes, Xiu Jun Wang, and Xiwen Tang

Précis: This seminal report advances knowledge about how the cytoprotective transcription factor Nrf2 mediates drug resistance in many cancers and how these effects can be overcome to improve outcomes.

Hsp27 Regulates Epithelial Mesenchymal Transition, Metastasis, and Circulating Tumor Cells in Prostate Cancer
Masaki Shiota, Jennifer L. Bishop, Ka Mun Nip, Anousheh Zardan, Ario Takeuchi, Thomas Cordonnier, Eliana Beraldi, Jenny Bazov, Ladan Fazli, Kim Chi, Martin Gleave, and Amina Zoubidi

Précis: Preclinical and clinical studies demonstrate the efficacy of targeting the chaperone Hsp27 in reducing metastases in prostate cancer, with potentially broader implications in human cancers generally where this molecule may support stem-like functions.

Novel Therapeutic Strategy to Prevent Chemotherapy-Induced Persistent Sensory Neuropathy By TRPA1 Blockade
Gabriela Trevisan, Serena Materazzi, Camilla Fusi, Alessandra Altomare, Giancarlo Aldini, Maura Lodovici, Riccardo Patacchini, Pierangelo Geppetti, and Romina Nassini

Précis: With an increasing number of cancer survivors, it is important for researchers to direct more attention to preventing or ameliorating the side-effects they suffer, such as chemotherapy-induced neuropathies that are as yet little understood or studied.

TUMOR AND STEM CELL BIOLOGY

Trop-2 Promotes Prostate Cancer Metastasis By Modulating β1 Integrin Functions
Marco Trerotola, Danielle L. Jernigan, Qin Liu, Javed Siddiqui, Alessandro Fatatis, and Lucia R. Languino

Précis: Targeting the transmembrane molecule Trop-2 may provide a route to block metastatic dissemination.

NEDD9 Depletion Destabilizes Aurora Kinase and Heights the Efficacy of Aurora A Inhibitors: Implications for Treatment of Metastatic Solid Tumors
Ryan J. Ice, Sarah L. McLaughlin, Ryan H. Livengood, Mark V. Culp, Erik R. Eddy, Alexey V. Ivanov, and Elena N. Pugacheva

Précis: Provocative findings suggest a rationale to use inhibitors of a mitotic regulatory kinase in treatment of metastatic tumors, with predicted sensitivities correlated to tumor expression of the prometastatic regulatory factor NEDD9.
β-Catenin/POU5F1/SOX2
Transcription Factor Complex
Mediates IGF-1 Receptor Signaling and
Predicts Poor Prognosis in Lung
Adenocarcinoma
Chuan Xu, Dan Xie, Shi-Cang Yu, Xiao-Jun Yang,
Li-Ru He, Jing Yang, Yi-Fang Ping, Bin Wang,
Lang Yang, Sen-Lin Xu, Wei Cui,
Qing-Liang Wang, Wen-Juan Fu, Qing Liu,
Cheng Qian, You-Hong Cui, Jeremy N. Rich,
Hsiang-Fu Kung, Xia Zhang, and Xiu-Wu Bian
Précis: This potentially seminal study reports a
novel complex that mediates self-renewal of
cancer stem-like cells in lung cancers and perhaps
other epithelial tumors.

ABOUT THE COVER
Rapid acquired resistance to antiangiogenic therapies such as bevacizumab
limits clinical utility of this approach in highly vascular tumors including
glioblastoma multiforme. β1 integrins represent a critical pathway for the
promotion of malignant progression and acquired therapy resistance in
cancer cells through adhesive interactions with the surrounding tumor
microenvironment. Using a multimodal approach, it was found that the β1
integrin subunit was functionally upregulated in patient glioblastoma
specimens with acquired resistance to bevacizumab. Knockdown or
inhibition of the β1 integrin subunit with neutralizing monoclonal antibodies
promoted reversion of malignant phenotype and attenuated in vivo growth of
bevacizumab-resistant glioblastoma xenografts. For details, see article by
Carbonell and colleagues on page 3145.