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

2965 Complex Tumor Genomes Inferred from Single Circulating Tumor Cells by Array-CGH and Next-Generation Sequencing
Ellen Heitzeler, Martina Auer, Christin Gasch, Martin Pichler, Peter Ull, Eva Maria Hoffmann, Sigurd Lax, Julie Waldisquield-Geiigl, Oliver Mauermann, Carolin Lackner, Gerald Hofler, Florian Eisner, Heinz Sill, Hellmut Samonigg, Klaus Pantel, Sabine Riedlhofer, Thomas Bauerhofer, Jochen B. Geiigl, and Michael R. Speicher

MICROENVIRONMENT AND IMMUNOLOGY

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

Précis: 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.

Précis: 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.

Précis: This study describes 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.

Précis: 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.
Adipocytes Cause Leukemia Cell Resistance to L-Asparaginase via Release of Glutamine

Ehsan A. Ehsanipour, Xia Sheng, James W. Behan, Xingchao Wang, Anna Butturini, Vassilios I. Avramis, and Steven D. Mittelman

Précis: Studies identify mechanisms behind the poor survival of obese leukemia patients through impaired asparaginase response.

Pancreatic Cancer-Associated Stellate Cells Promote Differentiation of Myeloid-Derived Suppressor Cells in a STAT3-Dependent Manner

Thomas A. Mace, Zeenath Ameen, Amy Collins, Sylwia Wojcik, Markus Mair, Gregory S. Young, James R. Fuchs, Tim D. Eubank, Wendy L. Frankel, Taniai Bekaii-Saab, Mark Bloomston, and Gregory B. Lesinski

Précis: 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.

Inhibition of Histone Demethylase JMJD1A Improves Anti-Angiogenic Therapy and Reduces Tumor-Associated Macrophages

Tsuyoshi Osawa, Rika Tsuchida, Masashi Muramatsu, Teppei Shimamura, Feng Wang, Jun-ichi Suehiro, Yasuharu Kanki, Youichiro Wada, Yasuhito Yuasa, Hiroyuki Ichihara, Hiroaki Asano, Kazunori Tsukuda, Nagio Takigawa, Katsumi Saito, Atsushi Kiyokawa, and Masahumi Shibuya

Précis: 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.

Cowden Syndrome-Related Mutations in PTEN Associate with Enhanced Proteasome Activity

Xin He, Nicholas Arrotta, Deepa Radhakrishnan, Yu Wang, Todd Romigh, and Charis Eng

Précis: 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.

Oncogenic NRAS, Required for Pathogenesis of Embryonic Rhabdomyosarcoma, Relies upon the HMGAI–IGFBP2 Pathway

Zhizhong Li, Yunyu Zhang, Krishnan Ramanujan, Yan Ma, David G. Kirsch, and David J. Glass

Précis: 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.

Acquired Resistance to EGFR Inhibitors Is Associated with a Manifestation of Stem Cell–like Properties in Cancer Cells

Kazuhiko Shien, Shinichi Toyooka, Hiromasa Yamamoto, Junichi Soto, Masaru Jida, Kelsie L. Thu, Shinshu Hashida, Yuho Maki, Eiki Ichihara, Hiroaki Asano, Kazunori Tsukuda, Nagio Takigawa, Katsumi Saito, Atsushi Kiyokawa, and Masahumi Shibuya

Précis: 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.

Novel HSP90 Inhibitor NVP-HSP990 Targets Cell-Cycle Regulators to Ablate Olig2-Positive Glioma Tumor–Initiating Cells

Jun Fu, Dimpy Koul, Jun Yao, Shuzhen Wang, Ying Yuan, Howard Colman, Erik. P. Sulman, Frederick. F. Lang, and W.K. Alfred Yung

Précis: 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.

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

Wenzin Xu, Monica Jones, Bai Liu, Xiaoyun Zhu, Christopher B. Johnson, Ana C. Edwards, Peter R. Rhode, and Hing C. Wong

Précis: Findings offer preclinical proof-of-concept for an engineered T-cell stimulant that mediates antitumor activity against multiple myeloma, rationalizing its clinical evaluation.
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, Younghun 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.

RXRα 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, Xi Jun Wang, and Xiuwen 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 Altmare, Giancarlo Aldini, Maura Lodovici, Riccardo Patacchini, Pierangelo Gepetti, 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.
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.