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**Cancer Research**

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### Breaking Advances

977  Highlights from Recent Cancer Literature

### Review

979  Light In and Sound Out: Emerging Translational Strategies for Photoacoustic Imaging
S. Zackrisson, S.M.W.Y. van de Ven, and S.S. Gambhir

### Priority Report

1005  Cell Lineage Tracing Reveals a Biliary Origin of Intrahepatic Cholangiocarcinoma

**Précis:** The findings from this preclinical study support an argument that the cell of origin of intrahepatic cholangiocarcinoma is able to arise from biliary epithelia, with potential therapeutic implications for this treatment-refractory cancer.

1045  PD-1 and Tim-3 Regulate the Expansion of Tumor Antigen–Specific CD8⁺ T Cells Induced by Melanoma Vaccines

**Précis:** These seminal results show how the administration of immune checkpoint inhibitors with cancer vaccines may vastly improve their antitumor efficacy, a harbinger of great promise for this type of active immunotherapy in cancer treatment.

### Microenvironment and Immunology

1011  Oligodendrocyte Progenitor Cells Promote Neovascularization in Glioma by Disrupting the Blood–Brain Barrier
Yujie Huang, Caitlin Hoffman, Prajwal Rajappa, Joon-Hyung Kim, Wenhuo Hu, Jason Huse, Zhongshu Tang, Xuri Li, Babette Weksler, Jacqueline Bromberg, David C. Lyden, and Jeffrey P. Greenfield

**Précis:** This important study reports the discovery of a novel stromal cell type in the brain tumor microenvironment that is crucial for vascular remodeling and neuroangiogenesis processes needed for brain tumor progression.

1022  GPR56 Inhibits Melanoma Growth by Internalizing and Degrading Its Ligand TG2
Liquan Yang, Scott Friedland, Nancy Corson, and Lei Xu

**Précis:** A tumor-promoting function of extracellular matrix that is found to be reversible might offer a therapeutic strategy for reprogramming the tumor microenvironment to assist in cancer control.

1032  Collagen Signaling Enhances Tumor Progression after Anti-VEGF Therapy in a Murine Model of Pancreatic Ductal Adenocarcinoma

**Précis:** This study identifies a new pathway induced by collagen I that stimulates tumor progression after anti-VEGF therapy.

1056  Accumulation of Cytosolic Calcium Induces Necroptotic Cell Death in Human Neuroblastoma
Motonari Nomura, Ayumi Ueno, Kotaro Saga, Masahiro Fukuzawa, and Yasufumi Kaneda

**Précis:** These findings define an upstream pathway for activation of the programmed necrosis process known as necroptosis, with potential therapeutic implications in cancer cells.
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1067  Inducible Nitric Oxide Synthase Drives mTOR Pathway Activation and Proliferation of Human Melanoma by Reversible Nitrosylation of TSC2  
Esther Lopez-Rivera, Padmini Jayaraman, Falguni Parikh, Michael A. Davies, Suhendan Ekmeckioglu, Sudeh Izadmehr, Denáí R. Milton, Jerry E. Chipuk, Elizabeth A. Grimm, Yeriel Estrada, Julio Aguirre-Ghiso, and Andrew G. Sikora  
Précis: These findings suggest new insights into how the mTOR pathway may be driven in cancer cells by nitrosylation of a key upstream activator, with clinical implications on how to improve melanoma therapy using NOS inhibitors.

1116  CRR9/CLPTM1L Regulates Cell Survival Signaling and Is Required for Ras Transformation and Lung Tumorigenesis  
Michael A. James, Haris G. Vikis, Everett Tate, Amy L. Rymaszewski, and Ming You  
Précis: These findings establish a protumorigenic role for a transmembrane protein that is critical for Ras-driven lung cancers, with potential implications for therapy and chemosensitization.

128  HuR Posttranscriptionally Regulates WEE1: Implications for the DNA Damage Response in Pancreatic Cancer Cells  
Précis: This study shows how pancreatic cancer cells protect themselves against DNA damage, offering possible insights into the resistance of this cancer to therapy and how its response to DNA damaging agents used as clinical therapeutics might be improved.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

1153  Prodigiosin Rescues Deficient p53 Signaling and Antitumor Effects via Upregulating p73 and Disrupting Its Interaction with Mutant p53  
Bo Hong, Varun V. Prabhu, Shengliang Zhang, A. Pieter J. van den Heuvel, David T. Dicker, Levy Kopelovich, and Wafik S. El-Deiry  
Précis: These findings suggest a rationale for a generalized strategy to treat human cancers by blocking a pivotal kinase-regulated step in mRNA translation.
The Niacin/Butyrate Receptor GPR109A Suppresses Mammary Tumorigenesis by Inhibiting Cell Survival

Précis: These results describe novel modes of action for niacin and butyrate in the mammary epithelium, where they activate a G protein–coupled receptor that suppresses tumorigenesis.

A Preclinical Model of CD38-Pretargeted Radioimmunotherapy for Plasma Cell Malignancies

Précis: This report offers a preclinical proof of concept for a novel radioimmunotherapy (PRIT) in a model of multiple myeloma, demonstrating rapid responses and achieving long-term survival.

Phosphorylation at Ser-181 of Oncogenic KRAS Is Required for Tumor Growth
Carles Barceló, Noelia Paco, Mireia Morell, Blanca Alvarez-Moya, Neus Bota-Rabassedas,Montserrat Jaumot, Felip Vilardell, Gabriel Capella, and Neus Agell

Précis: This important study presents one of the more important findings about KRAS structure and function in some years, with implications for a novel route to therapeutically attack KRAS-driven tumors.

Unbiased Compound Screening Identifies Unexpected Drug Sensitivities and Novel Treatment Options for Gastrointestinal Stromal Tumors
Sergei Boichuk, Derek J. Lee, Keith R. Mehallak, Kathleen R. Makielski, Agnieszka Wozniak, Danushka S. Seneviratne, Nina Korzeniewski, Rolando Cuevas, Joshua A. Parry, Matthew F. Brown, James Zewe, Takahiro Taguchi, Shin-Fan Kuan, Patrick Schoffski, Maria Debick-Rychter, and Anette Duensing

Précis: Gastrointestinal stromal tumor (GIST) cells that are resistant to Gleevec (imatinib) retain an unexpectedly high sensitivity to certain types of FDA-approved chemotherapeutic agents, an important discovery that prompts immediate clinical testing in patients with drug-resistant tumors.

Curcumin Targets Breast Cancer Stem–like Cells with Microtentacles That Persist in Mammospheres and Promote Reattachment
Monica S. Charpentier, Rebecca A. Whipple, Michele I. Vitolo, Amanda E. Boggs, Jana Slociv, Keyata N. Thompson, Lekhana Bhandary, and Stuart S. Martin

Précis: A tubulin-based cell surface protrusion on cancer stem–like cells mediates cell-surface and cell–cell attachment phenomena that may promote metastasis.
Tumor Suppressor Alterations Cooperate to Drive Aggressive Mesotheliomas with Enriched Cancer Stem Cells via a p53–miR-34a–c-Met Axis
Craig W. Menges, Yuvaraj Kadariya, Deborah Altomare, Jacqueline Talarchek, Erin Neumann-Domer, Yue Wu, Guang-Hui Xiao, Irina M. Shapiro, Vihren N. Kolev, Jonathan A. Pachter, Andres J. Klein-Szanto, and Joseph R. Testa

Précis: A genetically engineered mouse model of asbestos-induced carcinogenesis rapidly develops mesothelioma characterized by an aggressive cancer stem-like cell population that drives invasion and metastasis, offering a useful preclinical system for study.

High Fidelity Patient-Derived Xenografts for Accelerating Prostate Cancer Discovery and Drug Development

Précis: A panel of transplantable patient-derived xenografts of prostate cancer that captures their natural biologic and molecular heterogeneity offers a next-generation model to define the most effective personalized therapies.

Correction: Lenalidomide Inhibits Lymphangiogenesis in Preclinical Models of Mantle Cell Lymphoma

ABOUT THE COVER
TF-011-MMAE (HuMax-TF-ADC), an antibody-drug conjugate composed of a tissue factor-specific antibody, a protease-cleavable linker, and the microtubule disrupting agent monomethyl auristatin E, is a novel antitumor agent with promise as a broad-acting therapeutic in many types of human cancer. The antitumor activity of TF-011-MMAE is dependent on binding to tissue factor-positive tumor cells, followed by highly efficient internalization and lysosomal targeting, which allows intracellular release of the auristatin and subsequent tumor cell killing. After three hours of incubation with tissue factor-expressing ovarian cancer cells, TF-011 (green), the antibody backbone of TF-011-MMAE, colocalized with the lysosomal marker LAMP-1 (red). Colocalization of TF-011 and LAMP-1 (yellow) demonstrates that, upon target binding, TF-011 is rapidly targeted to the lysosomal compartment. For details, see article by Breij and colleagues on page 1214.