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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.

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 neoangiogenesis 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY
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.

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.

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.

American Association for Cancer Research
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**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

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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. Mehalek, 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 Schofski, Maria Debiec-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.

An Antibody–Drug Conjugate That Targets Tissue Factor Exhibits Potent Therapeutic Activity against a Broad Range of Solid Tumors

Précis: This study offers a preclinical proof of concept for a novel antitumor agent with promise as a broad-acting therapeutic in many types of human cancer.

Loss of Androgen Receptor Expression Promotes a Stem-like Cell Phenotype in Prostate Cancer through STAT3 Signaling
Anne Schroeder, Andreas Herrmann, Gregory Cherryholmes, Claudia Kowolik, Ralf Buettner, Sumanta Pal, Hua Yu, Gerhard Müller-Newen, and Richard Jove

Précis: These findings suggest that castrate-resistant prostate cancer dominated by stem-like cells may be particularly tractable to attack with antagonists of STAT3/IL-6 pathways.

Targeting a Glioblastoma Cancer Stem-Cell Population Defined by EGF Receptor Variant III
David R. Emlet, Puja Gupta, Marina Holgado-Madruga, Catherine A. Del Vecchio, Siddhartha S. Mitra, Shuang-Yin Han, Gordon Li, Kristin C. Jensen, Hannes Vogel, Linda Wei Xu, Stephen S. Skirboll, and Albert J. Wong

Précis: This work defines a mutated oncogene expressed in cancer stem-like cells in aggressive brain tumors, where it can be used to specifically target this cell population.

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 Slovic, 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.

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