

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**
Rachel V. Guest, Luke Boulter, Timothy J. Kendall, Sarah E. Minnis-Lyons, Robert Walker, Stephen J. Wigmore, Owen J. Sansom, and Stuart J. Forbes
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, Wenhua 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.

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

Kristina Y. Aguilera, Lee B. Rivera, Hoon Hur, Juliet G. Carbon, Jason E. Toombs, Courtney D. Goldstein, Michael T. Dellinger, Diego H. Castrillon, and Rolf A. Brekken

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**

Julien Fourcade, Zhaojun Sun, Ornella Pagliano, Joe-Marc Chauvin, Cindy Sander, Bratislav Janjic, Ahmad A. Tarhini, Hussein A. Tawbi, John M. Kirkwood, Stergios Moschos, Hong Wang, Philippe Guillaume, Immanuel F. Luescher, Arthur Krieg, Ana C. Anderson, Vijay K. Kuchroo, and Hassane M. Zarour

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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 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 Ekmekcioglu, Sudeh Izadmehr, Denái 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.*

1079 NUP98 Fusion Oncoproteins Promote Aneuploidy by Attenuating the Mitotic Spindle Checkpoint

Valentina Salsi, Silvia Ferrari, Paolo Gorello, Sebastian Fantini, Francesca Chiavolelli, Cristina Mecucci, and Vincenzo Zappavigna

Précis: *These findings suggest a mechanistic basis to grasp how an oncoprotein that promotes whole chromosome instability can cause acute myeloid leukemia, with implications for understanding the relationship between aneuploidy and cancer.*

1091 Activation of the NOTCH Pathway in Head and Neck Cancer



Wenyue Sun, Daria A. Gaykalova, Michael F. Ochs, Elizabeth Mambo, Demetri Arnaoutakis, Yan Liu, Myriam Loyo, Nishant Agrawal, Jason Howard, Ryan Li, Sun Ahn, Elana Fertig, David Sidransky, Jeffery Houghton, Kalyan Buddavarapu, Tiffany Sanford, Ashish Choudhary, Will Darden, Alex Adai, Gary Latham, Justin Bishop, Rajni Sharma, William H. Westra, Patrick Hennessey, Christine H. Chung, and Joseph A. Califano

Précis: *The results of this study imply that therapies that target the NOTCH pathway may be more widely suitable for head and neck cancer treatment than appreciated currently.*

1105 Identification of Alternative Splicing Events Regulated by the Oncogenic Factor SRSF1 in Lung Cancer

Fernando J. de Miguel, Ravi D. Sharma, María J. Pajares, Luis M. Montuenga, Angel Rubio, and Ruben Pio

Précis: *A novel genome-wide analytical tool was used in this study to define splicing events regulated by the oncogenic splicing factor SRSF1 in lung cancer, with implications for understanding how aberrant splicing drives cancer pathogenesis.*

1116 CRR9/CLPTMIL 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.*

1128 HuR Posttranscriptionally Regulates WEE1: Implications for the DNA Damage Response in Pancreatic Cancer Cells

Shruti Lal, Richard A. Burkhardt, Neil Beeharry, Vikram Bhattacharjee, Eric R. Londin, Joseph A. Cozzitorto, Carmella Romeo, Masaya Jimbo, Zoë A. Norris, Charles J. Yeo, Janet A. Sawicki, Jordan M. Winter, Isidore Rigoutsos, Timothy J. Yen, and Jonathan R. Brody

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.*

1141 Cyclin E1 Deregulation Occurs Early in Secretory Cell Transformation to Promote Formation of Fallopian Tube-Derived High-Grade Serous Ovarian Cancers



Alison M. Karst, Paul M. Jones, Natalie Vena, Azra H. Ligon, Joyce F. Liu, Michelle S. Hirsch, Dariush Etemadmoghadam, David D.L. Bowtell, and Ronny Drapkin

Précis: *These findings corroborate the hypothesis that dysregulation of a major S-phase cyclin drives transformation of fallopian tube secretory cells, which are now generally viewed as the main cell of origin for high-grade serous ovarian cancer.*

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.*

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- 1166** **The Niacin/Butyrate Receptor GPR109A Suppresses Mammary Tumorigenesis by Inhibiting Cell Survival**
Selvakumar Elangovan, Rajneesh Pathania, Sabarish Ramachandran, Sudha Ananth, Ravi N. Padia, Ling Lan, Nagendra Singh, Pamela M. Martin, Lesleyann Hawthorn, Puttur D. Prasad, Vadivel Ganapathy, and Muthusamy Thangaraju

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.*

- 1179** **A Preclinical Model of CD38-Pretargeted Radioimmunotherapy for Plasma Cell Malignancies**
Damian J. Green, Nural N. Orgun, Jon C. Jones, Mark D. Hylarides, John M. Pagel, Donald K. Hamlin, D.S. Wilbur, Yukang Lin, Darrell R. Fisher, Aimee L. Kenoyer, Shani L. Frayo, Ajay K. Gopal, Johnnie J. Orozco, Theodore A. Gooley, Brent L. Wood, William I. Bensinger, and Oliver W. Press

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.*

- 1190** **Phosphorylation at Ser-181 of Oncogenic KRAS Is Required for Tumor Growth**
Carles Barceló, Noelia Paco, Mireia Morell, Blanca Alvarez-Moya, Neus Bota-Rabasedas, 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.*

- 1200** **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 Schöffski, 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.*

- 1214** **An Antibody–Drug Conjugate That Targets Tissue Factor Exhibits Potent Therapeutic Activity against a Broad Range of Solid Tumors**

Esther C.W. Breij, Bart E.C.G. de Goeij, Sandra Verploegen, Danita H. Schuurhuis, Ali Amirkhosravi, John Francis, Vibeke Breinholt Miller, Mischa Houtkamp, Wim K. Bleeker, David Satijn, and Paul W.H.I. Parren

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.*

TUMOR AND STEM CELL BIOLOGY

- 1227** **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.*

- 1238** **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.*

- 1250** **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.*

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1261 Tumor Suppressor Alterations Cooperate to Drive Aggressive Mesotheliomas with Enriched Cancer Stem Cells via a p53–miR-34a–c-Met Axis

Craig W. Menges, Yuwaraj 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.

1272 High Fidelity Patient-Derived Xenografts for Accelerating Prostate Cancer Discovery and Drug Development

Dong Lin, Alexander W. Wyatt, Hui Xue, Yuwei Wang, Xin Dong, Anne Haegert, Rebecca Wu, Sonal Brahmabhatt, Fan Mo, Lina Jong, Robert H. Bell, Shawn Anderson, Antonio Hurtado-Coll, Ladan Fazli, Manju Sharma, Himisha Beltran, Mark Rubin, Michael Cox, Peter W. Gout, James Morris, Larry Goldenberg, Stanislav V. Volik, Martin E. Gleave, Colin C. Collins, and Yuzhuo Wang

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

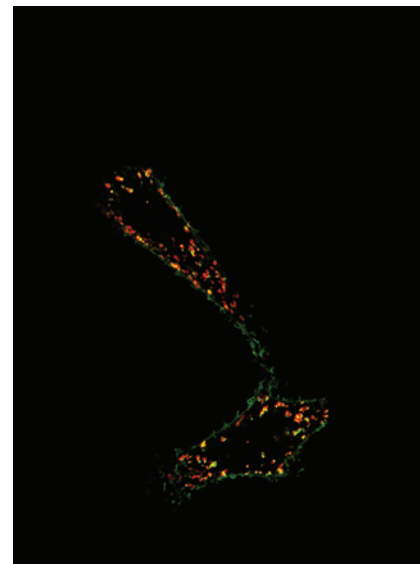
1284 Correction: Lenalidomide Inhibits Lymphangiogenesis in Preclinical Models of Mantle Cell Lymphoma

 AC icon indicates Author Choice

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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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