**REVIEWS**

**6295**  
Resuscitating Wild-Type p53 Expression by Disrupting Ceramide Glycosylation: A Novel Approach to Target Mutant p53 Tumors  
Yong-Yu Liu

**6300**  
Treatment of Hematologic Malignancies with Immunotoxins and Antibody-Drug Conjugates  
David J. FitzGerald, Alan S. Wayne, Robert J. Kreitman, and Ira Pastan

**PRIORITY REPORTS**

**6310**  
Regulator of G Protein Signaling 6 Mediates Doxorubicin-Induced ATM and p53 Activation by a Reactive Oxygen Species–Dependent Mechanism  
Jie Huang, Jianqi Yang, Riswanath Maity, Daisuke Mayuzumi, and Rory A. Fisher  
**Précis:** This study reveals a new mechanism for understanding the therapeutic activity of doxorubicin, identifying a mediator of its action as a target for cancer chemotherapy.

**6320**  
Long Noncoding RNA ROTAIR Regulates Polycomb-Dependent Chromatin Modification and Is Associated with Poor Prognosis in Colorectal Cancers  
Ryunosuke Kogo, Teppei Shimamura, Koshi Mimori, Kohichi Kawahara, Seiya Imoto, Tomoya Sudo, Fumiaki Tanaka, Kohbi Shibata, Akira Suzuki, Shizuo Komune, Satoru Miyano, and Masaki Mori  
**Précis:** Long noncoding RNAs that have been discovered recently represent an important emerging area of investigation in cancer pathobiology and epigenetics.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

**6327**  
Evolution of Tumor Invasiveness: The Adaptive Tumor Microenvironment Landscape Model  
Hyung-Ok Lee, Ariosto S. Silva, Susanna Concilio, Yue-Sheng Li, Michael Slifker, Robert A. Gatenby, and Jonathan D. Cheng  
**Précis:** In utilizing mathematical modeling to quantify tumor-microenvironment interactions, this study offers new insights into how stromal influences on cancer cell proliferation that are rewarded by the tumor landscape could be disrupted for therapeutic purposes.

**6338**  
**p38** Promotes Breast Cancer Cell Motility and Metastasis through Regulation of RhoC GTPase, Cytoskeletal Architecture, and a Novel Leading Edge Behavior  
**Précis:** Cell biological studies were combined with a novel computational mechanical modeling method to identify the molecular basis for leading edge behavior in motile breast cancer cells, with potential therapeutic implications.

**6350**  
Antiangiogenic Agent Sunitinib Transiently Increases Tumor Oxygenation and Suppresses Cycling Hypoxia  
Shingo Matsumoto, Sonny Batra, Keita Saito, Hironobu Yasui, Rajani Choudhuri, Chandramouli Gadisetti, Sankaran Subramanian, Nallathamby Devasahayam, Jeewa P. Munasinghe, James B. Mitchell, and Murali C. Krishna  
**Précis:** Using a noninvasive imaging method that can monitor tumor oxygenation, this study reveals a previously unappreciated mode of action for antiangiogenic agents used increasingly widely in the oncology clinic.
Activation of the Glucocorticoid Receptor Is Associated with Poor Prognosis in Estrogen Receptor-Negative Breast Cancer

Deng Pan, Masha Kocherginsky, and Suzanne D. Conzen

**Précis:** By identifying the glucocorticoid receptor as a key driver of central pathways of chemotherapy resistance and metastasis, this important study may help explain the basis for the poor prognosis of a subset of ER-negative breast cancers.

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Glioblastoma Angiogenesis and Tumor Cell Invasiveness Are Differentially Regulated by β8 Integrin

Jeremy H. Tchaicha, Steve B. Reyes, Jaekyung Shin, Mohammad G. Hossain, Frederick F. Lang, and Joseph H. McCarty

**Précis:** This mechanistic study reveals how autocrine activation of TGFβ signaling pathways by integrin β8 differentially regulates angiogenesis versus invasion in deadly brain tumors.

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TLR9 Agonists Oppositely Modulate DNA Repair Genes in Tumor versus Immune Cells and Enhance Chemotherapy Effects

Michele Sommariva, Loris De Cecco, Michelandrea De Cesare, Lucia Sfondrini, Sylvie Ménard, Cecilia Melani, Domenico Delia, Nadia Zaffaroni, Graziella Pratesi, Valentina Uva, Elda Tagliafuoe, and Andrea Balsari

**Précis:** Findings encourage clinical development of treatment protocols in which intratumoral injection of an immune stimulatory agent is combined with systemic DNA damaging therapies.

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Characterization of Chemokines and Adhesion Molecules Associated with T cell Presence in Tertiary Lymphoid Structures in Human Lung Cancer

Luc de Chaisemartin, Jéremy Goc, Diane Damotte, Pierre Validire, Pierre Magdelenaat, Marco Alfano, Isabelle Cremer, Wolf-Herman Fridman, Catherine Saudès-Fridman, and Marie-Caroline Dieu-Nosjean

**Précis:** This study identifies molecules that mediate migration of tumor-specific T cells into tertiary lymphoid structures where T cell priming occurs, suggesting new strategies to enhance the efficacy of cancer immunotherapy.

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Tumor-Associated Macrophages Mediate Immunosuppression in the Renal Cancer Microenvironment by Activating the 15-Lipoxygenase-2 Pathway

Irina Daurkin, Evgeniy Eruslanov, Taryn Gilbert, George Q. Perrin, Chester Algood, Scott M. Gilbert, Charles J. Rosser, Li-Ming Su, Johannes Vieweg, and Sergei Kusmartsev

**Précis:** Findings define a specific lipoxygenase that is essential for tumor-associated macrophages to nurture the tumor microenvironment by driving immune escape.

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IRF-1 Expression Is Essential for Natural Killer Cells to Suppress Metastasis

Antje Ksienzyk, Berit Neumann, Ramya Nandakumar, Katja Finsterbusch, Martina Grashoff, Rainer Zawatzky, Günter Bernhardt, Hansjörg Hauser, and Andreas Kröger

**Précis:** Tumoricidal natural killer cells are attracted to budding sites of metastasis by the tumor cells themselves, which by expressing the IFN-γ–regulated transcription factor IRF1 generate signals that reinforce immune surveillance and prevent effective colonization.

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Asialoglycoprotein Receptor Promotes Cancer Metastasis by Activating the EGFR-ERK Pathway

Suguru Ueno, Marija Mojic, Yoshimi Ohashi, Nobuaki Higashi, Yoshihiro Hayakawa, and Tatsuro Irimura

**Précis:** Hepatic lectins are a metastatic stimulus in the lung tumor microenvironment by acting as a positive modifier of EGFR-ERK signaling.

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Immune Adjuvant Efficacy of CpG Oligonucleotide in Cancer Treatment Is Founded Specifically upon TLR9 Function in Plasmacytoid Dendritic Cells


**Précis:** This study unravels the mechanistic basis for the immune adjuvant effects of CpG oligonucleotide, with implications on how to use it most effectively in combinatorial immunotherapy regimens.
MOLECULAR AND CELLULAR PATHOBIOLOGY

Enhancement of TGF-β Signaling Responses by the E3 Ubiquitin Ligase Arkadia Provides Tumor Suppression in Colorectal Cancer
Vikas Sharma, Anna G. Antonacopoulou, Shinya Tanaka, Alexis A. Panoutsopoulos, Vasiliki Bravou, Haralabos P. Kalofonos, and Vasso Episkopou

Précis: The definition of a ubiquitin ligase that determines the positive versus negative functions of transforming growth factor-β in colon cancer may advance understanding of its dual nature during tumorigenesis.

miR-152 Is a Tumor Suppressor microRNA That Is Silenced by DNA Hypermethylation in Endometrial Cancer
Tomohiko Tsuruta, Ken-ichi Kozaki, Atsushi Uesugi, Mayuko Furuta, Akira Hirasawa, Issei Imoto, Nobuyuki Susumu, Daisuke Aoki, and Johji Inazawa

Précis: The etiology and development of human cancers that are poorly understood may be enlightened by defining tumor suppressor microRNAs, as illustrated in this function-based screen in endometrial cancers.

Pivotal Role of Reduced let-7g Expression in Breast Cancer Invasion and Metastasis
Pengxu Qian, Zehua Zuo, Zhengsheng Wu, Xianyi Meng, Gaopeng Li, Zhengzhou Wu, Weijie Zhang, Sheng Tan, Vijay Pandey, Yandan Yao, Puyue Wang, Liqing Zhao, Jun Wang, Qiang Wu, Erwei Song, Peter E. Lobie, Zhinan Yin, and Tao Zhu

Précis: Only one of several let-7 miRNA family members serves as a prognostic biomarker in breast cancer that promotes breast cancer invasion and metastasis.

Loss of Transcription Factor KLF5 in the Context of p53 Ablation Drives Invasive Progression of Human Squamous Cell Cancer
Yizeng Yang, Hiroshi Nakagawa, Marie-Pier Tetreault, Janelle Billig, Noel Victor, Abha Goyal, Antonia R. Sepulveda, and Jonathan P. Katz

Précis: Findings identify a secondary event that cooperates with p53 mutation to drive malignant conversion of human squamous carcinomas.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Long-lived Inflammatory Signaling in Irradiated Bone Marrow Is Genome Dependent
Sally A. Lorimore, Debayan Mukherjee, Joanne I. Robinson, Jennifer A. Chrystal, and Eric G. Wright

Précis: This study suggests that radiation exposure produces a surprisingly durable procarcinogenic inflammatory effect that may differ on a genetic basis in different individuals, perhaps helping explain why some individuals are at greater risk of radiation-induced cancers than others despite similar initial levels of radiation-induced DNA damage.

Tissue Factor–Activated Coagulation Cascade in the Tumor Microenvironment Is Critical for Tumor Progression and an Effective Target for Therapy
Yuan Liu, Pengfei Jiang, Katerina Capkova, Dong Xue, Longwu Ye, Subhash C. Sinha, Nigel Mackman, Kim D. Janda, and Cheng Liu

Précis: Targeting the coagulation cascade activated in the tumor microenvironment may be a highly effective strategy for therapeutic eradication of metastatic cancer.

Intratumoral De Novo Steroid Synthesis Activates Androgen Receptor in Castration-Resistant Prostate Cancer and Is Upregulated by Treatment with CYP17A1 Inhibitors
Changmeng Cai, Sen Chen, Patrick Ng, Glenn J. Buhley, Peter S. Nelson, Elahe A. Mostaghel, Brett Marck, Alvin M. Matsumoto, Nicholas I. Simon, Hongyun Wang, Shaoyong Chen, and Steven P. Balk

Précis: In castration-resistant prostate cancers, the activity of the androgen receptor may still rely upon de novo steroid synthesis in the tumor, which may respond to therapies that can suppress this synthesis.
Oncogene AEG-1 Promotes Glioma-Induced Neurodegeneration by Increasing Glutamate Excitotoxicity
Seok-Geun Lee, Keetae Kim, Timothy P. Kegelman, Rupesh Dash, Swadesh K. Das, Jung Kyoungh Choi, Luni Emdad, Eric L. Howlett, Hyun Yong Jeon, Zhao Zhong Su, Byoung Kwon Yoo, Devanand Sarkar, Sung-Hoon Kim, Dong-Chul Kang, and Paul B. Fisher

Précis: By providing insights into how gliomas induce neurodegeneration, a hallmark of this deadly cancer, the findings suggest novel entry points for developing targeted therapies to improve its treatment.

6524

ZNF668 Functions as a Tumor Suppressor by Regulating p53 Stability and Function in Breast Cancer
Ruozhen Hu, Guang Peng, Hui Dai, Eun-Kyoung Breuer, Katherine Stemke-Hale, Kaiyi Li, Ana M. Gonzalez-Angulo, Gordon B. Mills, and Shiaw-Yih Lin

Précis: Genome-wide studies had identified the subject of this study previously as a frequently mutated gene in breast cancer, but its role and function in p53 control were unknown until now.

6535

Haploinsufficiency in the Prometastasis Kiss1 Receptor Gpr54 Delays Breast Tumor Initiation, Progression, and Lung Metastasis
Sung-Gook Cho, Ying Wang, Melissa Rodriguez, Kunrong Tan, Wenzheng Zhang, Jian Luo, Dali Li, and Mingyao Liu

Précis: Mice lacking the prometastatic receptor Kiss1R are resistant to breast cancer due to deficiencies in Rho signaling.

6547

A Role for Bone Morphogenetic Protein-4 in Lymph Node Vascular Remodeling and Primary Tumor Growth
Rae H. Farnsworth, Tara Karnezis, Ramin Shayan, Masataka Matsumoto, Cameron J. Nowell, Marc G. Achen, and Steven A. Stacker

Précis: This study identifies a TGFβ-related growth factor that negatively regulates aspects of the metastatic niche formation in tumor-draining lymph nodes, acting to control both seed and soil in the metastatic process.

ABOUT THE COVER

Breast tumor development in 7-week-old PyMT/Kiss1r+/− mouse. Whole mounting of the fourth inguinal mammary fat pad of 7-week-old PyMT/Kiss1r+/− mouse shows hyperplastic nodules. Kiss1r heterozygosity in MMTV-PyMT mouse reduced hyperplastic nodule numbers and delayed tumor initiation and formation. For details, see the article by Cho and colleagues on page 6535 of this issue.