

BREAKING ADVANCES

- 6293 | **Highlights from Recent Cancer Literature**

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, Biswanath 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 *HOTAIR* 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, Kohei 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 γ Promotes Breast Cancer Cell Motility and Metastasis through Regulation of RhoC GTPase, Cytoskeletal Architecture, and a Novel Leading Edge Behavior**
Devin T. Rosenthal, Harish Iyer, Silvia Escudero, Liwei Bao, Zhifen Wu, Alejandra C. Ventura, Celina G. Kleer, Ellen M. Arruda, Krishna Garikipati, and Sofia D. Merajver
- 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 Gadiseti, Sankaran Subramanian, Nallathamby Devasahayam, Jeeva 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.

6360

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.

6400

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.

6410

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 Andrea 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.

MICROENVIRONMENT AND IMMUNOLOGY

6371

Glioblastoma Angiogenesis and Tumor Cell Invasiveness Are Differentially Regulated by $\beta 8$ 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 TGF β signaling pathways by integrin $\beta 8$ differentially regulates angiogenesis versus invasion in deadly brain tumors.

6382

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 Tagliabue, 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.

6419

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.

6428

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

Stefan Nierkens, Martijn H. den Brok, Zacharias Garcia, Susan Togher, Jori Wagenaars, Melissa Wassink, Louis Boon, Theo J. Ruers, Carl G. Figdor, Stephen P. Schoenberger, Gosse J. Adema, and Edith M. Janssen

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 immunochemotherapy regimens.

6391

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

Luc de Chaisemartin, Jérémy Goc, Diane Damotte, Pierre Valdire, Pierre Magdeleinat, Marco Alifano, Isabelle Cremer, Wolf-Herman Fridman, Catherine Sautès-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.

6438 **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, Alexios 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.

6450 **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.

6463 **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.

6475 **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.

6485

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.

**THERAPEUTICS, TARGETS, AND
CHEMICAL BIOLOGY**

6492

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.

6503

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. Bubley, 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.

6514

Oncogene *AEG-1* Promotes Glioma-Induced Neurodegeneration by Increasing Glutamate Excitotoxicity

Seok-Geun Lee, Keetae Kim, Timothy P. Kegelmann, Rupesh Dash, Swadesh K. Das, Jung Kyoung 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.

TUMOR AND STEM CELL BIOLOGY

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 *TGF β* -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.

