

BREAKING ADVANCES

- 3437 | **Highlights from Recent Cancer Literature**

REVIEWS

- 3439 | **Regulatory T-cell Modulation Using Cyclophosphamide in Vaccine Approaches: A Current Perspective**
Dung T. Le and Elizabeth M. Jaffee
- 3445 | **Epstein–Barr Virus Infection as an Epigenetic Driver of Tumorigenesis**
Atsushi Kaneda, Keisuke Matsusaka, Hiroyuki Aburatani, and Masashi Fukayama

PRIORITY REPORTS

- 3451 | ***Fra-1* Promotes Breast Cancer Chemosensitivity by Driving Cancer Stem Cells from Dormancy**
Dan Lu, Si Chen, Xiaoyue Tan, Na Li, Chenghu Liu, Zongjin Li, Ze Liu, Dwayne G. Stupack, Ralph A. Reisfeld, and Rong Xiang
- Précis:* A relative of the transcription factor *Fos* is found to mediate a cancer stem cell–related function critical for metastatic progression of breast cancer, perhaps acting as a central transcriptional organizer given connections between *Fos* and cytosine methyltransferase activity in malignant transformation.
- 3457 | **Distinct Transcriptional Programs Mediated by the Ligand-Dependent Full-Length Androgen Receptor and Its Splice Variants in Castration-Resistant Prostate Cancer**
Rong Hu, Changxue Lu, Elahe A. Mostaghel, Srinivasan Yegnasubramanian, Meltem Gurel, Clare Tannahill, Joanne Edwards, William B. Isaacs, Peter S. Nelson, Eric Bluemn, Stephen R. Plymate, and Jun Luo
- Précis:* Androgen receptor splice variants exert different effects on transcriptional programs after therapeutic suppression of the full-length receptor, contributing to drug resistance in castration-resistant prostate cancer.

- 3463 | **Integrin $\alpha 5\beta 1$ Plays a Critical Role in Resistance to Temozolomide by Interfering with the p53 Pathway in High-Grade Glioma**

Hana Janouskova, Anne Maglott, David Y. Leger, Catherine Bossert, Fanny Noulet, Eric Guerin, Dominique Guenot, Sophie Pinel, Pascal Chastagner, François Plenat, Natacha Entz-Werle, Jacqueline Lehmann-Che, Julien Godet, Sophie Martin, Jan Teisinger, and Monique Dontenwill

Précis: Findings offer preclinical proof-of-concept for targeting $\alpha 5\beta 1$ integrin to improve the eradication of high-grade glioma expressing a functional p53 protein.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 3471 | **Kidney Tumor Biomarkers Revealed by Simultaneous Multiple Matrix Metabolomics Analysis**
Sheila Ganti, Sandra L. Taylor, Omran Abu Aboud, Joy Yang, Christopher Evans, Michael V. Osier, Danny C. Alexander, Kyoungmi Kim, and Robert H. Weiss
- Précis:* A comprehensive metabolomics analysis of multiple biofluids and tissues from a cancer xenograft model gives a fuller picture of metabolic changes that permit the identification of novel theranostic targets.
- 3480 | **Transcriptional Signatures of Ral GTPase Are Associated with Aggressive Clinicopathologic Characteristics in Human Cancer**
Steven C. Smith, Alexander S. Baras, Charles R. Owens, Garrett Dancik, and Dan Theodorescu
- Précis:* Findings advance understanding of the clinical significance of Ral GTPases in human cancer, with specific attention to how they can be used to predict outcomes in various tumor types and to aid in the development of Ral-targeted therapies.

3492 **Ultrasensitive Measurement of Hotspot Mutations in Tumor DNA in Blood Using Error-Suppressed Multiplexed Deep Sequencing**
Azeet Narayan, Nicholas J. Carriero, Scott N. Gettinger, Jeannie Kluytenaar, Kevin R. Kozak, Torunn I. Yock, Nicole E. Muscato, Pedro Ugarelli, Roy H. Decker, and Abhijit A. Patel
Précis: NextGen sequencing can be used to measure minute amounts of tumor-derived DNA in the blood, providing a tool to evaluate the diagnostic utility of circulating tumor DNA as a cancer biomarker.

3499 **CellMiner: A Web-Based Suite of Genomic and Pharmacologic Tools to Explore Transcript and Drug Patterns in the NCI-60 Cell Line Set**
William C. Reinhold, Margot Sunshine, Hongfang Liu, Sudhir Varma, Kurt W. Kohn, Joel Morris, James Doroshow, and Yves Pommier
Précis: This report describes a readily accessible Web-based application that opens for in silico discovery a huge NCI database built around genomic, epigenomic, and pharmacologic analyses of the NCI-60, a collection of 60 widely studied human cancer cell lines.

MICROENVIRONMENT AND IMMUNOLOGY

3512 **Deletion of the Endothelial Bmx Tyrosine Kinase Decreases Tumor Angiogenesis and Growth**
Tanja Holopainen, Vanessa López-Alpuche, Wei Zheng, Ritva Heljasvaara, Dennis Jones, Yun He, Denis Tvorogov, Gabriela D'Amico, Zoltan Wiener, Leif C. Andersson, Taina Pihlajaniemi, Wang Min, and Kari Alitalo
Précis: Findings offer preclinical support for therapeutic targeting of an arterial endothelial non-receptor tyrosine kinase as a novel antiangiogenic strategy for cancer treatment.

3522 **Fibroblast-Derived Dermal Matrix Drives Development of Aggressive Cutaneous Squamous Cell Carcinoma in Patients with Recessive Dystrophic Epidermolysis Bullosa**
Yi-Zhen Ng, Celine Pourreyaon, Julio C. Salas-Alanis, Jasbani H.S. Dayal, Rodrigo Cepeda-Valdes, Wenfei Yan, Sheila Wright, Mei Chen, Jo-David Fine, Fiona J. Hogg, John A. McGrath, Dedee F. Murrell, Irene M. Leigh, E. Birgit Lane, and Andrew P. South
Précis: The collagen composition of the extracellular matrix in skin is found to be a pivotal determinant of tumor formation in individuals with a genetic skin disease, who are prone to develop aggressive squamous carcinomas.

3535 **The Vitamin E Analogue α -TEA Stimulates Tumor Autophagy and Enhances Antigen Cross-Presentation**
Yuhuan Li, Tobias Hahn, Kendra Garrison, Zhi-Hua Cui, Andrew Thorburn, Jacqueline Thorburn, Hong-Ming Hu, and Emmanuel T. Akporiaye
Précis: Findings suggest a generalized method to improve antitumor immunity with the use of a vitamin E derivative as a supplement to cancer immunotherapy.

3546 **CXCR6 Upregulation Contributes to a Proinflammatory Tumor Microenvironment That Drives Metastasis and Poor Patient Outcomes in Hepatocellular Carcinoma**
Qiang Gao, Ying-Jun Zhao, Xiao-Ying Wang, Shuang-Jian Qiu, Ying-Hong Shi, Jian Sun, Yong Yi, Jie-Yi Shi, Guo-Ming Shi, Zhen-Bin Ding, Yong-Sheng Xiao, Zhong-Hua Zhao, Jian Zhou, Xiang-Huo He, and Jia Fan
Précis: This important study defines a pivotal chemokine regulator of inflammation in the microenvironment of human liver tumors, the blockade of which might limit invasion and metastasis and improve therapeutic outcomes.

3557 **The T-cell Receptor Repertoire of Tumor-Infiltrating Regulatory T Lymphocytes Is Skewed Toward Public Sequences**
Alexander Sainz-Perez, Annick Lim, Brigitte Lemerrier, and Claude Leclerc
Précis: This deep-sequencing analysis offers insights into how T-regulatory cells expand within the tumor microenvironment, where they blunt immunosurveillance during malignant progression, by suggesting the dominance of a relatively small number of T-cell clones.

3570 **IL-10 Directly Activates and Expands Tumor-Resident CD8⁺ T Cells without De Novo Infiltration from Secondary Lymphoid Organs**
Jan Emmerich, John B. Mumm, Ivan H. Chan, Drake LaFace, Hoa Truong, Terrill McClanahan, Daniel M. Gorman, and Martin Oft
Précis: In the absence of systemic immune activation or any contribution from lymphoid organs, IL-10 can uniquely activate and expand cytotoxic T cells within the tumor, where it may offer an immunotherapeutic option, challenging prevailing views of IL-10 as a tumor-supportive function.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 3582 **Cancer Angiogenesis Induced by Kaposi Sarcoma–Associated Herpesvirus Is Mediated by EZH2**
Meilan He, Wei Zhang, Thomas Bakken, Melissa Schutten, Zsolt Toth, Jae U. Jung, Parkash Gill, Mark Cannon, and Shou-Jiang Gao

Précis: By revealing how an oncogenic herpesvirus associated with an HIV-related skin tumor promotes tumor angiogenesis, this study suggests novel insights into the mechanisms of oncogenesis and novel strategies for antiangiogenic treatment.

- 3593 **ZNF217 Is a Marker of Poor Prognosis in Breast Cancer That Drives Epithelial–Mesenchymal Transition and Invasion**

Julie A. Vendrell, Aurélie Thollet, Nhan T. Nguyen, Sandra E. Ghayad, Stéphanie Vinot, Ivan Bièche, Evelyne Grisard, Véronique Josserand, Jean-Luc Coll, Pierre Roux, Laura Corbo, Isabelle Treilleux, Ruth Rimokh, and Pascale A. Cohen

Précis: A relatively uncharacterized zinc finger protein is shown to act as a prognostic biomarker in breast cancer, most likely through upregulation of epithelial–mesenchymal transition and promotion of metastases.

- 3607 **Wnt/Snail Signaling Regulates Cytochrome *c* Oxidase and Glucose Metabolism**

Su Yeon Lee, Hyun Min Jeon, Min Kyung Ju, Cho Hee Kim, Gyesoon Yoon, Song Iy Han, Hye Gyeong Park, and Ho Sung Kang

Précis: This study describes a novel function of the Wnt/Snail signaling pathway in the regulation of mitochondrial respiration and glycolytic switch that contributes to tumor progression.

- 3618 **miRNA-708 Control of CD44⁺ Prostate Cancer–Initiating Cells**

Sharanjot Saini, Shahana Majid, Varahram Shahryari, Sumit Arora, Soichiro Yamamura, Inik Chang, Mohd Saif Zaman, Guoren Deng, Yuichiro Tanaka, and Rajvir Dahiya

Précis: Findings identify a functional role for miR-708 in regulating the cancer stem-like cell marker CD44, with potentially important implications for understanding the progression and prognosis of many human cancers in which CD44⁺ stem-like cells have been implicated.

- 3631 **miR-103/107 Promote Metastasis of Colorectal Cancer by Targeting the Metastasis Suppressors DAPK and KLF4**

Hsin-Yi Chen, Yu-Min Lin, Hsiang-Ching Chung, Yaw-Dong Lang, Ching-Jung Lin, John Huang, Wei-Chi Wang, Feng-Mao Lin, Zhen Chen, Hsien-Da Huang, John Y.-J. Shyy, Jin-Tung Liang, and Ruey-Hwa Chen

Précis: This study defines the mechanisms through which a microRNA functions in potentiating multiple steps in metastasis in the colon, establishing a broad impact on this process and implicating it as a potential therapeutic target.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 3642 **Histone Deacetylase Inhibitors Influence Chemotherapy Transport by Modulating Expression and Trafficking of a Common Polymorphic Variant of the ABCG2 Efflux Transporter**

Agnes Basseville, Akina Tamaki, Caterina Ierano, Shana Trostel, Yvona Ward, Robert W. Robey, Ramanujan S. Hegde, and Susan E. Bates

Précis: This study of HDAC inhibitors suggests a widely applicable use for the first of this recently approved new class of drugs in improving the pharmacokinetics of cancer chemotherapeutics, with immediate implications for clinical testing.

- 3652 **Temporary Disruption of the Blood–Brain Barrier by Use of Ultrasound and Microbubbles: Safety and Efficacy Evaluation in Rhesus Macaques**
Nathan McDannold, Costas D. Arvanitis, Natalia Vykhodtseva, and Margaret S. Livingstone

Précis: This work describes a noninvasive method to safely enable drug delivery to brain tumors and other CNS diseases, addressing a major clinical challenge for development of targeted therapies in these settings.

TUMOR AND STEM CELL BIOLOGY

- 3664 **CD27 Signaling Increases the Frequency of Regulatory T Cells and Promotes Tumor Growth**

Christina Claus, Carsten Riether, Christian Schürch, Matthias S. Matter, Tamara Hilmenyuk, and Adrian F. Ochsenbein

Précis: Findings reveal how a TNF receptor superfamily member mediates tumor-promoting effects of the adaptive immune system, with implications for new immunotherapeutic strategies to target this receptor.

3677 **Proline Oxidase Promotes Tumor Cell Survival in Hypoxic Tumor Microenvironments**

Wei Liu, Kristine Glunde, Zaver M. Bhujwalla, Venu Raman, Anit Sharma, and James M. Phang

Précis: The induction of proline oxidase and proline catabolism under oxygen and/or glucose deprivation contributes to tumor cell survival, thereby providing a better understanding of tumor metabolic reprogramming beyond the Warburg Effect.

3687 **Accumulation of Multipotent Progenitors with a Basal Differentiation Bias during Aging of Human Mammary Epithelia**

James C. Garbe, Francois Pepin, Fanny A. Pelissier, Klara Sputova, Agla J. Fridriksdottir, Diana E. Guo, Rene Villadsen, Morag Park, Ole W. Petersen, Alexander D. Borowsky, Martha R. Stampfer, and Mark A. LaBarge

Précis: Although most preclinical research in cancer is conducted in young animal models, aging is the most important risk factor for human cancer, and elucidation of changes that occur in the tissue microenvironment during aging will lead to fundamental new insights yet to emerge.

LETTERS TO THE EDITOR

3702 **GLI1 Modulates EMT in Pancreatic Cancer—Letter**

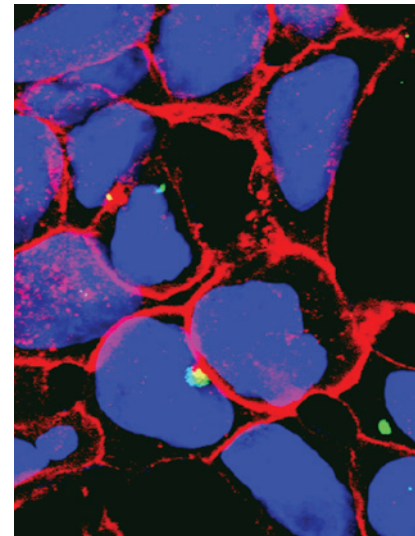
Shingo Inaguma, Kenji Kasai, Mitsuyoshi Hashimoto, and Hiroshi Ikeda

3704 **GLI1 Modulates EMT in Pancreatic Cancer—Response**

Simon Joost, Luciana L. Almada, Verena Rohhalter, Philipp S. Holz, Maite G. Fernandez-Barrena, Martin E. Fernandez-Zapico, and Matthias Lauth

ABOUT THE COVER

Rescue of a common ABCG2 variant by the HDAC inhibitor romidepsin. While the drug efflux transporter ABCG2 is expressed at the cell surface in transfected Flp-In-293 cells, its Q141K variant is trapped in the aggresome, an intracellular structure where misfolded proteins accumulate. Flp-In-293 cells expressing the Q141K variant were treated with romidepsin for 24 h, after which, immunofluorescence staining was done for ABCG2 (red), the aggresome marker γ -tubulin (green), and nuclei (blue). Romidepsin induced a drastic change in variant protein localization, from aggresome to the cell surface. This was accompanied by an increase in expression and a restoration of ABCG2-mediated drug efflux activity. For details, see article by Basseville and colleagues on page 3642 of this issue.



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