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

3457 Distinct Transcriptional Programs Mediated by the Ligand-Dependent Full-Length Androgen Receptor and Its Splice Variants in Castration-Resistant Prostate Cancer

INTEGRATED SYSTEMS AND TECHNOLOGIES

3463 Integrin α5β1 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 Noutel, Eric Guerin, Dominique Guenot, Sophie Pinel, Pascal Chastagner, Francois 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 α5β1 integrin to improve the eradication of high-grade glioma expressing a functional p53 protein.

3468 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.

3473 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.
Ultrasensitive Measurement of Hotspot Mutations in Tumor DNA in Blood Using Error-Suppressed Multiplexed Deep Sequencing

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.

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.

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 Tyvorgov, 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.

Fibroblast-Derived Dermal Matrix Drives Development of Aggressive Cutaneous Squamous Cell Carcinoma in Patients with Recessive Dystrophic Epidermolysis Bullosa
Yi-Zhen Ng, Celine Fourreyron, Julio C. Salas-Alanis, Jashmini H.S. Dayal, Rodrigo Cepeda-Valdes, Wenfeng 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.

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.

CXCR6 Uregulation 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, Ji-Zhi 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.

The T-cell Receptor Repertoire of Tumor-Infiltrating Regulatory T Lymphocytes Is Skewed Toward Public Sequences
Alexander Sainz-Perez, Annick Lim, Brigitte Lemercier, 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.

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, Hao 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

Precis: 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

Precis: 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

Precis: 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 Shahyari, Sumit Arora, Soichiro Yamamura, Inik Chang, Mohd Saif Zaman, Guoren Deng, Yuichiro Tanaka, and Rajvir Dahiya

Precis: 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

Precis: 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, Yvonna Ward, Robert W. Robey, Ramananjan S. Hegde, and Susan E. Bates

Precis: 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

Precis: 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 Schirch, Matthias S. Matter, Tamara Hillmenyk, and Adrian F. Ochsenbein

Precis: 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.
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.

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.

GLI1 Modulates EMT in Pancreatic Cancer—Letter
Shingo Inaguma, Kenji Kasai, Mitsuyoshi Hashimoto, and Hiroshi Ikeda

GLI1 Modulates EMT in Pancreatic Cancer—Response

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.