BREAKING ADVANCES

6097 Highlights from Recent Cancer Literature

REVIEWS

6099 RSK Isoforms in Cancer Cell Invasion and Metastasis
Florian J. Sulzmaier and Joe W. Ramos

6106 The Evolution of Melanoma Resistance Reveals Therapeutic Opportunities
Meghna Das Thakur and Darrin D. Stuart

PERSPECTIVES

6111 Formalizing an Integrative, Multidisciplinary Cancer Therapy Discovery Workflow
Mary F. McGuire, Heiko Enderling, Dorothy I. Wallace, Jaspreet Batra, Marie Jordan, Sushil Kumar, John C. Panetta, and Eddy Pasquier

6118 Redox Imbalance and Biochemical Changes in Cancer
Tonia C. Jorgenson, Weixiong Zhong, and Terry D. Oberley

MEETING REPORT

6124 Twenty-fifth Annual Pezcoller Symposium: Metabolism and Tumorigenesis
William Kaelin, David Livingston, Massimo Loda, Karen Vousden, and Enrico Mihich

PRIORITY REPORT

6128 A Comparative Genomic Approach for Identifying Synthetic Lethal Interactions in Human Cancer
Ramaesh Deshpande, Michael K. Asiedu, Mitchell Klebig, Shari Sutor, Elena Kuzmin, Justin Nelson, Jeff Piotrowski, Seung Ho Shin, Minori Yoshida, Michael Costanzo, Charles Boone, Dennis A. Wigle, and Chad L. Myers

PRÉCIS: Using the robust genetics of yeast, this study reveals new interactions between cancer-associated mutations in humans, leading to the identification of new candidate drug targets for suppressor functions widely deficient in cancers.

INTEGRATED SYSTEMS AND TECHNOLOGIES

6149 Novel Modeling of Cancer Cell Signaling Pathways Enables Systematic Drug Repositioning for Distinct Breast Cancer Metastases
Hong Zhao, Guangxin Jin, Kemi Cui, Ding Ren, Timothy Liu, Peikai Chen, Solomon Wong, Fuhai Li, Yubo Fan, Angel Rodriguez, Jenny Chang, and Stephen TC Wong

PRÉCIS: A generally applicable modeling method based on integrative cancer biology is used to uncover tactics for repositioning existing drugs, with the potential to immediately improve treatments for advanced cancer.

6164 Optical Metabolic Imaging Identifies Glycolytic Levels, Subtypes, and Early-Treatment Response in Breast Cancer
Alex J. Walsh, Rebecca S. Cook, H. Charles Manning, Donna J. Hicks, Alec Lafontant, Carlos L. Arteaga, and Melissa C. Skala

PRÉCIS: Optical imaging can rapidly assess how cellular metabolism responds to molecular alterations and drug action, offering a tool to accelerate drug development.

MICROENVIRONMENT AND IMMUNOLOGY

6175 Integrin αvβ3 and Fibronectin Upregulate Slug in Cancer Cells to Promote Clot Invasion and Metastasis
Lynn M. Knowles, Lisa A. Gurski, Charlotte Engel, James R. Gnarra, Jodi K. Maranchie, and Jan Pilch

PRÉCIS: These findings establish a mechanism through which cancer cells can colonize blood clots in the lung vasculature, potentially explaining why certain tumors, such as renal carcinomas and soft tissue sarcomas, have a proclivity for lung metastasis.
Targeting FSTL1 Prevents Tumor Bone Metastasis and Consequent Immune Dysfunction
Chie Kudo-Saito, Takafumi Fuwa, Kouichi Murakami, and Yutaka Kawakami

Precis: These important findings offer preclinical proof-of-concept for an attractive therapeutic target to prevent or treat bone metastasis, in part through a unique mechanism that can degrade an immune escape barrier erected by tumor cells.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Carboxyl-Terminal Modulator Protein Positively Regulates Akt Phosphorylation and Acts as an Oncogenic Driver in Breast Cancer

Precis: These results address some controversy in the field by corroborating the concept that an Akt-binding molecule promotes Akt phosphorylation and functions as an oncogenic molecule in breast cancer.

GPR116, an Adhesion G-Protein–Coupled Receptor, Promotes Breast Cancer Metastasis via the Gαq-p63RhoGEF-Rho GTPase Pathway
Xiaolong Tang, Rongrong Jin, Guojun Qu, Xiu Wang, Zhenxi Li, Zengjin Yuan, Chen Zhao, Stefan Siwko, Tieliu Shi, Ping Wang, Jiannr Xiao, Mingyao Liu, and Jian Luo

Precis: Identification of a G-protein coupled receptor that is crucial for the metastasis of breast cancer cells has implications for prognostics and targeting of advanced forms of human breast cancer.

Novel Oncogenic PDGFRA Mutations in Pediatric High-Grade Gliomas
Barbara S. Paugh, Xiaoyan Zhu, Chunxu Qu, Raelene Endersby, Alexander K. Diaz, Junyuan Zhang, Dorine A. Bax, Diana Carvalho, Rui M. Reis, Araz Omar-Thomas, Alberto Broniscer, Cynthia Wetmore, Jinghui Zhang, Chris Jones, David W. Ellison, and Suzanne J. Baker

Precis: These results suggest that there is a distinct spectrum of PDGF receptor alpha mutations in adult and pediatric cancers, with implications for etiology and therapy.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Tumor Cells Upregulate Normoxic HIF-1α in Response to Doxorubicin
Yiting Cao, Joseph M. Eble, Ejung Moon, Hong Yuan, Douglas H. Weitzel, Chelsea D. Landon, Charleen Yu-Chih Nien, Gabi Hanna, Jeremy N. Rich, James M. Provenzale, and Mark W. Dewhirst

Precis: This study suggests a means to optimize strategies for doxorubicin treatment by inhibiting the drug’s ability to upregulate HIF-1α under normoxic conditions (an unusual finding).

Erlotinib Resistance in Lung Cancer Cells Mediated by Integrin β3/Src/Akt-Driven Bypass Signaling
Rina Kanda, Akihiko Kawahara, Kosuke Watari, Yuichi Murakami, Kahori Sonoda, Masashi Maeda, Hideaki Fujita, Masayoshi Kage, Hidetaka Uramoto, Carlota Costa, Michihiko Kuwano, and Mayumi Ono

Precis: Acquired resistance to cancer cell–targeted therapies invariably poses clinical problems for resolution due to the inherent heterogeneity and plasticity of all human tumors, but combining agents that anticipate common resistance pathways may make it possible to delay relapses.

EGFR-Activating Mutations Correlate with a Fanconi Anemia–like Cellular Phenotype That Includes PARP Inhibitor Sensitivity
Heike N. Pflaflle, Meng Wang, Liliana Gheorghiu, Natalie Ferraiolo, Patricia Greninger, Kerstin Borgmann, Jeffrey Settleman, Cyril H. Benes, Leica V. Sequist, Lee Zou, and Henning Willers

Precis: These findings reveal mechanisms underlying cisplatin and PARP inhibitor sensitivity of EGFR-mutant lung cancer, potentially yielding therapeutic opportunities for further individualization of therapy in this subset of patients.

BRD4 Sustains Melanoma Proliferation and Represents a New Target for Epigenetic Therapy
Miguel F. Segura, Bárbara Fontanals-Cirera, Avital Gaziel-Sovran, María V. Guijarro, Doug Hanniford, Guangtao Zhang, Pilar González-Gomez, Marta Morante, Luz Jubierre, Weiija Zhang, Farbod Darvishian, Michael Ohlmeyer, Iman Osman, Ming-Ming Zhou, and Eva Hernandez

Precis: These findings strengthen a rationale for epigenetic treatment of melanomas based on pharmacologic targeting of a core transcriptional program that sustains melanoma cell identity.
**TUMOR AND STEM CELL BIOLOGY**

**Epithelial–Mesenchymal Transition and Tumor Suppression Are Controlled by a Reciprocal Feedback Loop between ZEB1 and Grainyhead-like-2**
Benjamin Cieply, Joshua Farris, James Denvir, Heide L. Ford, and Steven M. Frisch

**Precis:** A feedback loop between an activator of EMT and a repressor of EMT sets up a restriction point that must be breached by an overwhelming confluence of microenvironmental factors in order for a tumor cell to undergo EMT.

**Targeting Sonic Hedgehog-Associated Medulloblastoma through Inhibition of Aurora and Polo-like Kinases**
Shirley L. Markant, Lourdes Adriana Espanza, Jesse Sun, Kelly L. Barton, Lisa M. McCoig, Gerald A. Grant, John R. Crawford, Michael L. Levy, Paul A. Northcott, David Shih, Marc Remke, Michael D. Taylor, and Robert J. Wechsler-Reya

**Precis:** This study identifies a critical vulnerability in some pediatric medulloblastomas that is well suited to therapeutic attack by inhibiting pivotal G2-M phase cell-cycle kinases.

**Histone Acetyltransferase PCAF Is Required for Hedgehog-Gli-Dependent Transcription and Cancer Cell Proliferation**
Martina Malatesta, Cornelia Steinhauser, Faizan Mohammad, Deo P. Pandey, Massimo Squatrito, and Kristian Helin

**Precis:** These results define an important cofactor for a signaling pathway commonly activated in certain brain cancers, suggesting its relevance as a candidate therapeutic target.

**PLA2R1 Mediates Tumor Suppression by Activating JAK2**
David Vindrieux, Arnaud Augert, Christophe A. Girard, Delphine Gitenay, Helene Lallet-Daher, Clotilde Wiel, Benjamin Le Calvé, Baptiste Gras, Mylène Perrand, Stéphanie Verbeke, Yvan de Launoit, Xavier Leroy, Alain Puisieux, Sébastien Aubert, Michael Perrais, Michael Gelb, Hélène Simonnet, Gérard Lambau, and David Bernard

**Precis:** This study offers provocative findings in suggesting that Jak2 inhibitors currently in clinical trials may exert protumorigenic activity in some contexts.

**Activation of MAPK Pathways due to DUSP4 Loss Promotes Cancer Stem Cell-like Phenotypes in Basal-like Breast Cancer**
Justin M. Balko, Luis J. Schwartz, Neil E. Bhola, Richard Kurupi, Phillip Owens, Todd W. Miller, Henry Gómez, Rebecca S. Cook, and Carlos L. Arteaga

**Precis:** These findings support the clinical evaluation of MEK and JNK pathway inhibitors in treatment of aggressive triple-negative breast cancers.

**Interleukin-6 Is Required for Pancreatic Cancer Progression by Promoting MAPK Signaling Activation and Oxidative Stress Resistance**
Yaqing Zhang, Wei Yan, Meredith A. Collins, Filip Bednar, Sabita Rakshit, Bruce R. Zetter, Ben Z. Stanger, Ivy Chung, Andrew D. Rhim, and Marina Pasca di Magliano

**Precis:** These findings suggest that the cytokine IL-6 may be essential for progression of precursor lesions in pancreatic cancer, with therapeutic implications for how to improve treatment of this deadly disease.

**Correction:**

**Correction: Rational Drug Redesign to Overcome Drug Resistance in Cancer Therapy: Imatinib Moving Target**

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ABOUT THE COVER

The prognosis and quality of life of patients with breast cancer brain metastases is generally poor and there is no effective treatment. A generally applicable computational model integrated with systems biology experiments was developed and applied to reposition existing drugs that would inhibit brain metastases. Ten repositioned drug candidates with potential brain permeability were identified. In xenograft models, sunitinib (approved for treating advanced renal cell carcinoma and gastrointestinal stromal tumors) and dasatinib (approved for treating chronic myelogenous leukemia) were repositioned to prevent metastatic outgrowth of breast cancer cells in the brain. For details, see article by Zhao and colleagues on page 6149.
Cancer Research

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