BREAKING ADVANCES

Highlights from Recent Cancer Literature

REVIEWS

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

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

PERSPECTIVES

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

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

MEETING REPORT

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

PRIORITY REPORT

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

MICROENVIRONMENT AND IMMUNOLOGY

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

Specific Recruitment of γδ Regulatory T Cells in Human Breast Cancer
Jian Ye, Chunling Ma, Fang Wang, Eddy C. Hsueh, Karoly Toth, Yi Huang, Wei Mo, Shuai Liu, Bing Han, Mark A. Varvares, Daniel F. Holl, and Guangyong Peng

Ret: These findings rationalize the use of IL-10 antibodies to block migration of a class of T- regulatory cells into the breast cancer microenvironment, thereby derepressing the activity of antitumor T cells.

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

Novel Modeling of Cancer Cell Signaling Pathways Enables Systematic Drug Repositioning for Distinct Breast Cancer Metastases
Hong Zhao, Guangxu Jin, Kemi Cui, D impression. Timothy Liu, Peikai Chen, Solomon Wong, Fu Hai Li, Yibo Fan, Angel Rodriguez, Jenny Chang, and Stephen TC Wong

Ret: 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.

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

Ret: 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 predilection for lung metastasis.
**MOLECULAR AND CELLULAR PATHOBIOLOGY**

6185

**Targeting FSTL1 Prevents Tumor Bone Metastasis and Consequent Immune Dysfunction**
Chie Kudo-Saito, Takafumi Fuwa, Kouichi Murakami, and Yutaka Kawakami

**Précis:** 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.

6194

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

**Précis:** 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.

6206

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

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

6219

**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 Omur-Thomas, Alberto Broniscer, Cynthia Wetmore, Jinghui Zhang, Chris Jones, David W. Ellison, and Suzanne J. Baker

**Précis:** 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.

6230

**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

**Précis:** 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).

6243

**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

**Précis:** 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.

6254

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

**Précis:** 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.

6264

**BRD4 Sustains Melanoma Proliferation and Represents a New Target for Epigenetic Therapy**
Miguel F. Segura, Barbara Fontanals-Cirera, Avital Gaziel-Sovran, Maria 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

**Précis:** These findings strengthen a rationale for epigenetic treatment of melanomas based on pharmacologic targeting of a core transcriptional program that sustains melanoma cell identity.
NSD2 Is Recruited through Its PHD Domain to Oncogenic Gene Loci to Drive Multiple Myeloma
Zheng Huang, Haiping Wu, Shannon Chuai, Fiona Xu, Feng Yan, Nathan Englund, Zhaofu Wang, Hailong Zhang, Ming Fang, Youzhen Wang, Justin Gu, Man Zhang, Teddy Yang, Kehao Zhao, Yanyuan Yu, Jingquan Dai, Wei Yi, Shaoliang Zhou, Qian Li, Jing Wu, Jun Liu, Xu Wu, Homan Chan, Chris Lu, Peter Atadja, En Li, Yan Wang, and Min Hu

Precis: These findings deepen insights into how to target a transcription factor activated in multiple myeloma by a genetic translocation, with more general implications on how to attack this molecular class of targets.

Integrative Radiogenomic Profiling of Squamous Cell Lung Cancer

Precis: Genomic and epigenomic predictors of cancer radiosensitivity have remained frustratingly elusive, a challenge addressed here by a more highly integrative marker study than has been advanced previously.

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 undermine 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. McCooig, Gerald A. Grant, John B. 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, Faizaan 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 Ferrand, Stéphanie Verbeke, Yvan de Launoit, Xavier Leroy, Alain Puisieux, Sébastien Aubert, Michael Perrais, Michael Gelb, Hélène Simonnet, Gérard Lambeau, 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-negatives 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 Carlos L. Arteaga

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.

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