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### Highlights from Recent Cancer Literature

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### RSK Isoforms in Cancer Cell Invasion and Metastasis

Florian J. Sulzmaier and Joe W. Ramos

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### The Evolution of Melanoma Resistance Reveals Therapeutic Opportunities

Meghna Das Thakur and Darrin D. Stuart

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## PERSPECTIVES

### Formalizing an Integrative, Multidisciplinary Cancer Therapy Discovery Workflow

Mary F. McGuire, Heiko Enderling, Dorothy I. Wallace, John C. Panetta, and Eddy Pasquier

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### Redox Imbalance and Biochemical Changes in Cancer

Tonia C. Jorgenson, Weixiong Zhong, and Terry D. Oberley

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## MEETING REPORT

### Twenty-fifth Annual Pezcoller Symposium: Metabolism and Tumorigenesis

William Kaelin, David Livingston, Massimo Loda, Karen Vousden, and Enrico Milich

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## PRIORITY REPORT

### A Comparative Genomic Approach for Identifying Synthetic Lethal Interactions in Human Cancer

Raamesh 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

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### Specific Recruitment of \( \gamma \delta \) 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

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## CLINICAL STUDIES

### Novel Modeling of Cancer Cell Signaling Pathways Enables Systematic Drug Repositioning for Distinct Breast Cancer Metastases

Hong Zhao, Guangxu Jin, Kemi Cui, Ding Ren, Timothy Liu, Peikai Chen, Solomon Wong, Fuhai Li, Yubo Fan, Angel Rodriguez, Jenny Chang, and Stephen TC Wong

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### 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

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### Integrin \( \alpha v \beta 3 \) 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

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### Integulin \( \alpha v \beta 3 \) and \( \alpha v \beta 6 \) Are Novel Disparities of Pericyte and Smooth Muscle Cells in the Arterial Wall of Patients with Accelerated Vascular Disease

Samer Al-Dhalimy, Charles J. Van Dijk, Takashi Suzuki, Takahiro Morimoto, Scott R. Taylor, and Peter H. Helpern

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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.

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 Gqα-p63RhoGEF-Rho GTPase Pathway
Xiaolong Tang, Rongrong Jin, Guojun Qu, Xiu Wang, Zhenxi Li, Zengjin Yuan, Chen Zhao, Stefan Siwko, Tielu Shi, Ping Wang, Jianru 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 prognosis 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, Arzu Omur-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.

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 β1/Src/Akt-Driven Bypass Signaling
Rina Kanda, Akihiko Kawahara, Kosuke Watari, Yuichi Murakami, Kahori Sonoda, Masashi Maeda, Hideaki Fujita, Masayoshi Kage, Hidekata 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. Pfaffle, Meng Wang, Liliana Gheorghiu, Natalie Ferraiolo, Patricia Greninger, Kerstin Borgmann, Jeffrey Settleman, Cyril H. Benes, Levia 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-Sorran, Maria V. Guijarro, Doug Hannifold, Guangtao Zhang, Pilar González-Gomez, Marta Morante, Luz Jubierré, WeiJia Zhang, Farbod Darvishian, Michael Ohlmeyer, Iman Osman, Ming-Ming Zhou, and Eva Hernando

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.
NSD2 Is Recruited through Its PHD Domain to Oncogenic Gene Loci to Drive Multiple Myeloma
Zheng Huang, Haiping Wu, Shannon Chuai, Fiana Xu, Feng Yan, Nathan Englund, Zhaofu Wang, Hailong Zhang, Ming Fang, Youzhen Wang, Justin Gu, Man Zhang, Teddy Yang, Kehao Zhao, Yanyan Yu, Jingquan Dai, Wei Yi, Shaolian Zhou, Qian Li, Jing Wu, Jun Liu, Xu Wu, Homan Chan, Chris Lu, Peter Atadja, En Li, Yan Wang, and Min Hu
Preced: 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
Preced: 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
Preced: 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 Esparza, 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
Preced: This study identifies a critical vulnerability in some pediatric medulloblastomas that is well suited to therapeutic attack by inhibiting pivotal G_{2-M} phase cell-cycle kinases.

Histone Acetyltransferase PCAF Is Required for Hedgehog–Gil-Dependent Transcription and Cancer Cell Proliferation
Martina Malatesta, Cornelia Steinhauser, Faizaan Mohammad, Deo P. Pandey, Massimo Squatrito, and Kristian Helin
Preced: 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 Ferrais, Michael Gelb, Hélène Simonnet, Gérard Lambeau, and David Bernard
Preced: 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
Preced: 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 Massimo Squatrito
Preced: 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: 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.