Highlights from Recent Cancer Literature

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

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

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. Holi, and Guangyong Peng

Precise: 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.

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

Precise: 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.

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

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

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

Precise: 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.
### MOLECULAR AND CELLULAR PATHOBIOLOGY

#### 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.

#### 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, Jinru 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.

#### Novel Oncogenic PDGFRα Mutations in Pediatric High-Grade Gliomas

Barbara S. Paugh, Xiaoyan Zhu, Chunxu Qu, Raelene Endersby, Alexander K. Diaz, Junyujuan Zhang, Dorine A. Bax, Diana Carvalho, Rui M. Reis, Arau Omar-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 PDGFRα receptor alpha mutations in adult and pediatric cancers, with implications for etiology and therapy.

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#### 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

**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).

#### 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.

#### 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, Leica 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.

#### BRD4 Sustains Melanoma Proliferation and Represents a New Target for Epigenetic Therapy

Miguel F. Segura, Barbara Fontanals-Cirera, Avital Gaziel-Sorban, Maria V. Guijarro, Doug Hanniford, Guangtuo Zhang, Pilar González-Gomez, Marta Morante, Luz Jubierre, Weiija Zhang, Farbod Darvishian, Michael Ohlmeyer, Iman Osman, Ming-Ming Zhou, and Eva Hernando

**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.
**TUMOR AND STEM CELL BIOLOGY**

### 6277 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, Yanyan Yu, Jingquan Dai, Wei Yi, Shaolian Zhou, Qian Li, Jing Wu, Jun Liu, Xi Wu, Homan Chan, Chris Lu, Peter Atadja, En Li, Yan Wang, and Min Hu

**Précis:** 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.

### 6289 Integrative Radiogenomic Profiling of Squamous Cell Lung Cancer

**Précis:** 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.

### 6299 Epithelial–Mesenchymal Transition and Tumor Suppression Are Controlled by a Reciprocal Feedback Loop between ZEB1 and Grainyhead-like-2
Benjamin Cieply, Joshua Farris, James Denviri, Heide L. Ford, and Steven M. Frisch

**Précis:** 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.

### 6300 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 R. Crawford, Michael L. Levy, Paul A. Northcott, David Shih, Marc Remke, Michael D. Taylor, and Robert J. Wechsler-Reya

**Précis:** 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.

### 6310 Histone Acetyltransferase PCAF Is Required for Hedgehog–Gil-Dependent Transcription and Cancer Cell Proliferation
Martina Malatesta, Cornelia Steinhaeuer, Faizaan Mohammad, Deo P. Pandey, Massimo Squatrito, and Kristian Helin

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

### 6311 PLA2R1 Mediates Tumor Suppression by Activating JAK2
David Vindrieux, Arnaud Augert, Christophe A. Girard, Delphine Gittenay, 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

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

### 6312 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. Bhoia, Richard Kurupi, Phillip Owens, Todd W. Miller, Henry Gómez, Rebecca S. Cook, and Carlos L. Arteaga

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

### 6313 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 Peter Atadja

**Précis:** 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.