-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
Raamesh Deshpande, Michael K. Asiedu, Mitchell Klebig, Shari Sutor, Elena Kuzmin, Justin Nelson, Jeff Piotrowski, Seung Ho Shin, Minoru Yoshida, Michael Costanzo, Charles Boone, Dennis A. Wigle, and Chad L. Myers

Precis: 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.

-MICROENVIRONMENT AND IMMUNOLOGY-

6155 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. Maranche, and Jan Pilch

Precis: 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.
Targeting FSTL1 Prevents Tumor Bone Metastasis and Consequent Immune Dysfunction
Chie Kudo-Saito, Takaomi 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.

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 Gq/63RhoGEF-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

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 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 Onar-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.

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 β1/Src/Akt-Driven Bypass Signaling
Rina Kanda, Akihiko Kawahara, Kosuke Watari, Yuichi Murakami, Kahori Sonoda, Masashi Maeda, Hideaki Fujita, Masayoshi Kage, Hitetaka 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-Sovran, Maria V. Guijarro, Doug Hanniford, Guangtou Zhang, Pilar González-Gómez, 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.
Targeting Sonic Hedgehog-Associated Epithelial
Integrative Radiogenomic Profiling of NSD2 Is Recruited through Its PHD Domain to Oncogenic Gene Loci to Drive Multiple Myeloma

6289


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.

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.

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.

TUMOR AND STEM CELL BIOLOGY

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.

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

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

Precis: These results define an important cofactor for a tumor cell to undergo EMT.

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.

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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.