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Optical Metabolic Imaging Identifies Glycolytic Levels, Subtypes, and Early-Treatment Response in Breast Cancer
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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

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.

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.
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, 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 Onar-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. Pfaffle, Meng Wang, Liliana Gheorghiu, Natalie Ferraiolo, Patricia Greninger, Kerstin Borgmann, Jeffrey Settleman, Cyril H. Benes, Lecia 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 Hanniford, Guangtuo Zhang, Pilar González-Gomez, Marta Morante, Luz Jubierre, Weiija 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.
Targeting Sonic Hedgehog-Associated 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

Integrative Radiogenomic Profiling of Squamous Cell Lung Cancer

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

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

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

PLA2R1 Mediates Tumor Suppression by Activating JAK2
David Vindrieux, Arnaud Augert, Christophe A. Girard, Delphine Gitenay, Helene Lallet-Daher, Clotilde Wieil, 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

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Benjamin Cieply, Joshua Farris, James Denvir, Heide L. Ford, and Steven M. Frisch

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

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

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