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Cancer Research

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- 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
- Précis:* 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.

CLINICAL STUDIES

- 6137 | **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. Hoft, and Guangyong Peng
- Précis:* 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.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 6149 | **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
- Précis:* 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.
- 6164 | **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
- Précis:* Optical imaging can rapidly assess how cellular metabolism responds to molecular alterations and drug action, offering a tool to accelerate drug development.

MICROENVIRONMENT AND IMMUNOLOGY

- 6175 | **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
- Précis:* 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 carcinoma and soft tissue sarcomas, have a proclivity for lung metastasis.

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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6194

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

Yu-Peng Liu, Wen-Chi Liao, Luo-Ping Ger, Jiun-Chin Chen, Tai-I Hsu, Yu-Cheng Lee, Hong-Tai Chang, Yu-Chia Chen, Yi-Hua Jan, Kuen-Haur Lee, Yu-Hao Zeng, Michael Hsiao, and Pei-Jung Lu

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 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

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, 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

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 β1/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. Pfäffle, 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, Bárbara Fontanals-Cirera, Avital Gaziel-Sovran, María V. Guijarro, Doug Hanniford, Guangtao Zhang, Pilar González-Gomez, Marta Morante, Luz Jubierre, Weijia 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.

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, Xu 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**

Mohamed E. Abazeed, Drew J. Adams, Kristen E. Hurov, Pablo Tamayo, Chad J. Creighton, Dmitriy Sonkin, Andrew O. Giacomelli, Charles Du, Daniel F. Fries, Kwok-Kin Wong, Jill P. Mesirov, Jay S. Loeffler, Stuart L. Schreiber, Peter S. Hammerman, and Matthew Meyerson

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.

6323

Histone Acetyltransferase PCAF Is Required for Hedgehog–Gli-Dependent Transcription and Cancer Cell Proliferation

Martina Malatesta, Cornelia Steinhauer, 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.

6334

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

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

6346

Activation of MAPK Pathways due to DUSP4 Loss Promotes Cancer Stem Cell-like Phenotypes in Basal-like Breast Cancer

Justin M. Balko, Luis J. Schwarz, Neil E. Bhola, 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.

6359

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 Marina Pasca di Magliano

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.

TUMOR AND STEM CELL BIOLOGY

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 Denvir, 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.

6310

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

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.

CORRECTION

6375

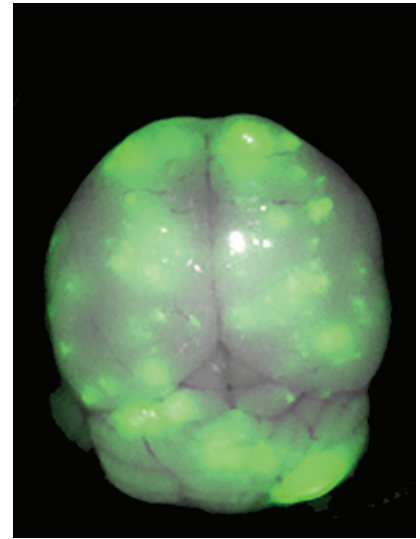
Correction: Rational Drug Redesign to Overcome Drug Resistance in Cancer Therapy: Imatinib Moving Target

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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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