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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.

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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.

CLINICAL STUDIES

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, Fuhui Li, Yubo Fan, Angel Rodriguez, Jenny Chang, and Stephen T.C. 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.

6149  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.

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. 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 carcinomas and soft tissue sarcomas, have a proclivity for lung metastasis.

INTEGRATED SYSTEMS AND TECHNOLOGIES

6164  A Comparative Genomic Approach for Identifying Synthetic Lethal Interactions in Human Cancer
      Raamesh Deshpande, Michael K. Asiedu, Mitchell Kleibig, 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.

MICROENVIRONMENT AND IMMUNOLOGY

6175  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

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 carcinomas and soft tissue sarcomas, have a proclivity for lung metastasis.
### 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

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<td>Carboxyl-Terminal Modulator Protein Positively Regulates Akt Phosphorylation and Acts as an Oncogenic Driver in Breast Cancer</td>
<td>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</td>
<td><strong>Précis:</strong> 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.</td>
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<td>6206</td>
<td>GPR116, an Adhesion G-Protein–Coupled Receptor, Promotes Breast Cancer Metastasis via the Gqα-p63RhoGEF-Rho GTPase Pathway</td>
<td>Xiaolong Tang, Rongrong Jin, Guojun Qu, Xiu Wang, Zhenzi Li, Zengjin Yuan, Chen Zhao, Stefan Siwko, Tieliu Shi, Ping Wang, Jianru Xiao, Mingyao Liu, and Jian Luo</td>
<td><strong>Précis:</strong> 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.</td>
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<td>6219</td>
<td>Novel Oncogenic PDGFRα Mutations in Pediatric High-Grade Gliomas</td>
<td>Barbara S. Paugh, Xiaoyan Zhu, Chunxu Qu, Raelene Endersby, Alexander K. Diaz, Junyuan Zhang, Dorina A. Bax, Diana Carvalho, Rui M. Reis, Arza Omar-Thomas, Alberto Broniscer, Cynthia Wetmore, Jinghui Zhang, Chris Jones, David W. Ellison, and Suzanne J. Baker</td>
<td><strong>Précis:</strong> 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.</td>
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### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

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<td>6230</td>
<td>Tumor Cells Upregulate Normoxic HIF-1α in Response to Doxorubicin</td>
<td>Yiting Cao, Joseph M. Ehle, Eujung 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</td>
<td><strong>Précis:</strong> 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).</td>
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<td>6243</td>
<td>Erlotinib Resistance in Lung Cancer Cells Mediated by Integrin β1/Src/Akt-Driven Bypass Signaling</td>
<td>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</td>
<td><strong>Précis:</strong> 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.</td>
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<td>6254</td>
<td>EGFR-Activating Mutations Correlate with a Fanconi Anemia–like Cellular Phenotype That Includes PARP Inhibitor Sensitivity</td>
<td>Heike N. Pfaffle, Meng Wang, Liliana Gheorghiu, Natalie Ferraiolo, Patricia Greniger, Kerstin Borgmann, Jeffrey Settleman, Cyril H. Benes, Lea V. Sequist, Lee Zou, and Henning Willers</td>
<td><strong>Précis:</strong> 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.</td>
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<td>6264</td>
<td>BRD4 Sustains Melanoma Proliferation and Represents a New Target for Epigenetic Therapy</td>
<td>Miguel F. Segura, Bárbara Fontanals-Cirera, Avital Gaziel-Sorran, Maria 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</td>
<td><strong>Précis:</strong> These findings strengthen a rationale for epigenetic treatment of melanomas based on pharmacologic targeting of a core transcriptional program that sustains melanoma cell identity.</td>
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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, Zhaoou Wang, Haitong Zhang, Ming Fang, Youzhen Wang, Justin Gu, Man Zhang, Teddy Yang, Kehao Zhao, Yanyan Yu, Jingquan Dai, Wei Yi, Shaoliang Zhou, Qian Li, Jing Wu, Jun Liu, Xia Wu, Homan Chan, Chris Lu, Peter Atadja, En Li, Yan Wang, and Min Hu

Precise: 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

Precise: 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

Precise: 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 Espanza, Jesse Sun, Kelly L. Barton, Lisa M. McCoiq, Gerald A. Grant, John R. Crawford, Michael L. Levy, Paul A. Northcott, David Shih, Marc Remke, Michael D. Taylor, and Robert J. Wechsler-Reya

Precise: This study identifies a critical vulnerability in some pediatric medulloblastomas that is well suited to therapeutic attack by inhibiting pivotal G1-M phase cell-cycle kinases.

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

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

Precise: 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 Perrais, Michel Gelb, Hélène Simonnet, Gérard Lambeau, and David Bernard

Precise: 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, Neel E. Bhola, Richard Kurupi, Phillip Owens, Todd W. Miller, Henry Gómez, Rebecca S. Cook, and Carlos L. Arteaga

Precise: 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 Marina Pasca di Magliano

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

CORRECTION
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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