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<td>Therapies with Diverse Mechanisms of Action Kill Cells by a Similar Exponential Process in Advanced Cancers</td>
<td>Krastan B. Blagoev, Julia Wilkerson, Wilfred D. Stein, James Yang, Susan E. Bates, and Tito Fojo</td>
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<td>Resistance to Chemotherapy: Patient Variability and Cellular Heterogeneity</td>
<td>David A. Kessler, Robert H. Austin, and Herbert Levine</td>
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**Priority Report**

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**Meeting Report**

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Immediate Utility of Two Approved Agents to Target Both the Metabolic Mevalonate Pathway and Its Restorative Feedback Loop
Aleksandra Pandya, Peter J. Mullen, Manpreet Kalkar, Rosemary Yu, Janice T. Pong, Zhihua Li, Suzanne Trudel, Karl S. Lang, Mark D. Minden, Aaron D. Schimmer, and Linda Z. Penn

Précis: This article provides an excellent illustration of polypharmacology discovery by tapping the existing armamentarium of approved drugs to identify immediately tractable new experimental therapies for clinical evaluation.

AMPK Reverses the Mesenchymal Phenotype of Cancer Cells by Targeting the Akt–MDM2–Foxo3a Signaling Axis
Chih-Chien Chou, Kuen-Haur Lee, I-Lu Lai, Dasheng Wang, Xiaokui Mo, Samuel K. Kulp, Charles L. Shapiro, and Ching-Shih Chen

Précis: This work illuminates a mechanism of EMT limitation in cancer cells, along with preclinical support for a tractable therapeutic strategy to reverse mesenchymal phenotypes associated with invasion and metastasis.

Neuronal Pentraxin 2 Supports Clear Cell Renal Cell Carcinoma by Activating the AMPA-Selective Glutamate Receptor-4
Christina A. von Roemeling, Derek C. Radisky, Laura A. Marlow, Simon J. Cooper, Stefan K. Grebe, Panagiotis Z. Anastasiadis, Han W. Tun, and John A. Copland

Précis: A secreted protein exclusively studied in the context of neuronal cell function appears to act through a calcium signaling pathway to support the pathogenicity of deadly kidney cancers, with immediate implications for a possible clinical treatment strategy.

Pyrvinium Attenuates Hedgehog Signaling Downstream of Smoothened
Bin Li, Dennis Liang Fei, Colin A. Flaveny, Nadia Dahmane, Valerie Baubet, Zhiqiang Wang, Feng Bai, Xin-Hai Pei, Jezaibel Rodriguez-Blanco, Brian Hang, Darren Orton, Lu Han, Baolin Wang, Anthony J. Capobianco, Ethan Lee, and David J. Robbins

Précis: An FDA-approved pinworm drug with potent activity as a casein kinase-1α agonist is found to robustly inhibit Hedgehog signaling in tumors, including those resistant to existing Hedgehog pathway inhibitors, with immediate implications for clinical testing.

Definition of PKC-α, CDK6, and MET as Therapeutic Targets in Triple-Negative Breast Cancer
Yi-Hsin Hsu, Jun Yao, Li-Chuan Chan, Ting-Jung Wu, Jennifer L. Hsu, Yueh-Fu Fang, Yongkun Wei, Yun Wu, Wen-Chien Huang, Chien-Liang Liu, Yuan-Ching Chang, Ming-Yang Wang, Chia-Wei Li, Jia Shen, Mei-Kuang Chen, Aysegul A. Sahin, Anil Sood, Gordon B. Mills, Dihua Yu, Gabriel N. Hortobagyi, and Mien-Chie Hung

Précis: These findings define three kinases critical for growth of an aggressive subtype of breast cancer, offering a preclinical rationale to target their activity as an effective therapy.

Mutant IDH1-Driven Cellular Transformation Increases RAD51-Mediated Homologous Recombination and Temozolomide Resistance
Shigeo Ohba, Joydeep Mukherjee, Wendy L. See, and Russell O. Pieper

Précis: Mutation of a key metabolic contributor to glioma development indirectly enhances homologous recombination-based repair of DNA damage triggered by the chemotherapy drug temozolomide, offering an explanation for the intrinsic resistance of gliomas to this drug and a rational path forward toward their eradication.

The RAC1 P29S Hotspot Mutation in Melanoma Confers Resistance to Pharmacological Inhibition of RAF
Ian R. Watson, Liren Li, Peter K. Cabeceiras, Mozdeh Mahdavi, Tony Gutschner, Giannicola Genovese, Guocan Wang, Zhaungna Fang, James M. Tepper, Katherine Stemke-Hale, Kenneth Y. Tsai, Michael A. Davies, Gordon B. Mills, and Lynda Chin

Précis: This timely report suggests a novel predictive biomarker for the efficacious response of melanoma patients to BRAF inhibitors, the most effective use of which has yet to be fully elucidated.
Epigenetic States of Cells of Origin and Tumor Evolution Drive Tumor-Initiating Cell Phenotype and Tumor Heterogeneity
Kin-Hoe Chow, Dong-Mi Shin, Molly H. Jenkins, Emily E. Miller, David J. Shi, Seungbum Choi, Benjamin E. Low, Vivek Philip, Brad Rybinski, Roderick T. Bronson, Michael D. Taylor, and Kyuson Yun

Précis: This study probes the sources of tumor heterogeneity, a core research challenge that—despite its recognition by clinical pathologists for many years and its recent rediscovery by molecular geneticists—still represents the chief weakness of all cancer cell-targeted therapeutic strategies.

TRIM29 Suppresses TWIST1 and Invasive Breast Cancer Behavior

Précis: TRIM29 exerts complex roles in cancer, but in breast cancer it appears to function as a tumor suppressor by suppressing a core regulator of the epithelial–mesenchymal transition, a pivotal step in driving invasive and metastatic behavior.

TRIB1 Supports Prostate Tumorigenesis and Tumor-Propagating Cell Survival by Regulation of Endoplasmic Reticulum Chaperone Expression
Tetsuo Mashima, Taeko Soma-Nagae, Toshiro Migita, Ryoko Kinoshita, Atsushi Iwamoto, Takeshi Yuasa, Junji Yonese, Yuichi Ishikawa, and Hiroyuki Seimiya

Précis: Prostate cancer stem-like cells appear to be addicted to oncogenic signals from an endoplasmic reticulum-dependent stress response pathway, a finding with potential therapeutic implications.

IDH1 R132H Mutation Generates a Distinct Phospholipid Metabolite Profile in Glioma
Morteza Esmaeili, Bob C. Hamans, Anna C. Navis, Remco van Horssen, Tone F. Bathe, Ingrid S. Gribbestad, William P. Leenders, and Arend Heerschap

Précis: This study reports novel noninvasive biomarkers of IDH1-mutant gliomas that may help to guide treatments to target aberrant metabolism in these aggressive brain tumors.

IL15RA Drives Antagonistic Mechanisms of Cancer Development and Immune Control in Lymphocyte-Enriched Triple-Negative Breast Cancers
Pierfrancesco Marra, Sumi Mathew, Anita Grigoriadis, Yin Wu, Fernanda Kyle-Cezar, Johnathan Watkins, Mamunur Rashid, Emanuele De Rinaldis, Sonya Hessey, Patrycja Gazinska, Adrian Hayday, and Andrew Tutt

Précis: Expression of an immune memory-inducing receptor in some triple-negative breast cancers, usually only expressed by T cells, may offer a mechanistic explanation for the paradoxical association of some of these high-grade tumors with better survival outcomes.

Epigenetic Targeting of Ovarian Cancer Stem Cells
Yinu Wang, Horacio Cardenas, Fang Fang, Salvatore Condello, Pietro Taverna, Matthew Segar, Yunlong Liu, Kenneth P. Nephew, and Daniela Matei

Précis: These results suggest that epigenome-targeting strategies can reprogram residual cancer stem-like cells to a differentiated state, thereby helping prevent the development of recurrent, chemoresistant disease.

Live-Cell Imaging of Invasion and Intravasation in an Artificial Microvessel Platform
Andrew D. Wong and Peter C. Searson

Précis: An artificial microvessel platform can be used to obtain striking images and mechanistic insights into how cancer cells invade the local microenvironment and enter and exit vessels, providing a new tool to help unravel the complexities of metastasis and its prevention and treatment.

LETTERS TO THE EDITOR

A Synthetic Lethality-Based Strategy to Treat Cancers Harboring a Genetic Deficiency in the Chromatin Remodeling Factor BRG1—Letter
Kenneth W. Thompson, Stefanie B. Marquez, and David Reisman

Proposal for a Synthetic Lethality Therapy Using the Paralog Dependence of Cancer Cells—Response
Takahiro Oike, Hideaki Ogihara, Takashi Nakano, and Takashi Kohno
CORRECTIONS

4950 Correction: The TGFβ–miR200–Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors

4951 Correction: Chk2 Phosphorylation of Survivin-ΔEx3 Contributes to a DNA Damage–Sensing Checkpoint in Cancer

ABOUT THE COVER

Confocal microscopy analysis for osteopontin performed on myeloid-derived suppressor cells (MDSC) shows osteopontin (red) localized under the cellular membrane but not colocalized with the ER marker concanavalin A (green) in MDSC. This picture is suggestive of the existence of an intracellular form, rather than a secreted form of osteopontin, in MDSC. For details, see article by S. Sangaletti and colleagues on page 4706.