Précis: Global assessment of tyrosine phosphorylation, coupled with functional screens, is used to identify tyrosine kinases driving cell growth and survival in sarcoma, thereby offering insight into new therapeutic strategies for these deadly tumors.

AMPKα Modulation in Cancer Progression: Multilayer Integrative Analysis of the Whole Transcriptome in Asian Gastric Cancer

Yon Hui Kim, Han Liang, Xiuping Liu, Ju-Seog Lee, Jae Yong Cho, Jae-Ho Cheong, Hognuen Kim, Min Li, Thomas J. Downey, Matthew D. Dyer, Yongming Sun, Jingtao Sun, Ellen M. Beasley, Hyun Cheol Chung, Sung Hoon Noh, John N. Weinstein, Chang-Gong Liu, and Garth Powis

Précis: The requirement for c-Src in tumor invasion evoked by oncogenic Ras has implications for the development of therapies to target the Ras pathway, long a goal of the field.

MICROENVIRONMENT AND IMMUNOLOGY

Cyclophosphamide Creates a Receptive Microenvironment for Prostate Cancer Skeletal Metastasis

Serk In Park, Jinhui Liao, Janice E. Berry, Xin Li, Amy J. Koh, Megan E. Michalski, Matthew R. Eber, Fabiana N. Soki, David Sadler, Sudha Sud, Sandra Tisdelle, Stephanie D. Daignault, Jeffrey A. Nemeth, Linda A. Snyder, Thomas J. Wronska, Kenneth J. Pienta, and Laurie K. McCauley

Précis: The chemotherapeutic drug cyclophosphamide, used in the treatment of many kinds of cancer, is found unexpectedly to exert a prometastatic effect within bone.
### Hepatocyte–Stellate Cell Cross-Talk in the Liver Engenders a Permissive Inflammatory Microenvironment That Drives Progression in Hepatocellular Carcinoma

Cédric Coulouarn, Anne Corlu, Denise Glaise, Isabelle Guénon, Snorri S. Thorgeirsson, and Bruno Clément

*Précis:* Molecular characterization of the cross-talk between cell types in the liver plays a major role in the progression of hepatocellular carcinoma and may offer novel therapeutic targets for epigenetic modulation.

### Kras Induces a Src/PEAK1/ErbB2 Kinase Amplification Loop That Drives Metastatic Growth and Therapy Resistance in Pancreatic Cancer

Jonathan A. Kelber, Theresa Reno, Sharmeeza Kausalal, Cristina Metildi, Tracy Wright, Konstantin Stol etov, Jessica M. Weems, Frederick D. Park, Evangeline Mose, Yingchun Wang, Robert M. Hoffman, Andrew M. Lowy, Michael Bouvet, and Richard L. Klemke

*Précis:* In serving as a novel diagnostic and prognostic biomarker in pancreatic ductal carcinoma, the novel tyrosine kinase PEAK1 may mediate cancer progression and multiple therapy-resistant phenotypes and thus represents an important new therapeutic target.

### Mitochondrial Bcl-2 Family Dynamics Define Therapy Response and Resistance in Neuroblastoma

Kelly C. Goldsmith, Michelle Gross, Susan Peirce, Dena Luyindula, Xuexuan Liu, Annette Vu, Michael Slozberg, Bong Guo, Huaying Zhao, C. Patrick Reynolds, and Michael D. Hogarty

*Précis:* Mitochondrial profiling reveals that acquired therapy resistance in neuroblastoma is due to repression at the level of Bax/Bak-mediated apoptosis, and this may offer a basis to stratify patients who could benefit most from treatment with Bcl-2/Bcl-xL antagonists.
Activation of Ras/PI3K/ERK Pathway Induces c-Myc Stabilization to Upregulate Argininosuccinate Synthetase, Leading to Argininosuccinate Deiminase Resistance in Melanoma Cells

Wen-Bin Tsai, Isamu Aiba, Yan Long, Hui-Kuan Lin, Lynn Feun, Niramol Savaraj, and Macus Tien Kuo

Precise: Findings offer mechanistic insight into how resistance emerges to arginine deprivation therapy and how inhibitors of the Ras/ERK and PI3K/AKT pathways might restore therapeutic responses.

Mitochondria-Targeted Drugs Synergize with 2-Deoxyglucose to Trigger Breast Cancer Cell Death

Gang Cheng, Jacek Zielonka, Brian P. Dranka, Donna McAllister, A. Craig Mackinnon Jr, Joy Joseph, and Balaraman Kalyanaraman

Precise: This important study may crack the long-standing challenge of how to employ the glycolytic inhibitor 2-deoxyglucose for generalized anticancer therapy, by combining it with mitochondria-targeted cationic compounds that can improve cancer cell cytotoxicity without toxic liabilities to normal tissue.

Smac Mimetic LBW242 Sensitizes XIAP-Overexpressing Neuroblastoma Cells for TNF-α-Independent Apoptosis

Georg Eschenburg, Angelika Egger, Alexander Schramm, Holger N. Losle, and Patrick Hundsdoerfer

Precise: Smac mimetics offer a potential adjuvant approach to sensitize or re sensitize tumors to chemotherapy, as illustrated by this preclinical proof-of-concept study in a commonly deadly type of pediatric cancer.

Epidermal Growth Factor Receptor Variant III Contributes to Cancer Stem Cell Phenotypes in Invasive Breast Carcinoma

Catherine A. Del Vecchio, Kristin C. Jensen, Ryan T. Nitta, A. Hunter Shain, Craig P. Giacomini, and Albert J. Wong

Precise: By identifying breast cancer stem cells that express a variant EGFR receptor, this study has implications for how to improve treatment for patients who harbor this variant receptor.

HER3 is Required for HER2-Induced Preneoplastic Changes to the Breast Epithelium and Tumor Formation

David B. Vaught, Jamie C. Stanford, Christian Young, Donna J. Hicks, Frank Wheeler, Cammie Rinehart, Violeta Sánchez, John Koland, William J. Muller, Carlos L. Arteaga, and Rebecca S. Cook

Precise: Findings offer a preclinical proof-of-concept for a new strategy to treat or prevent HER2-amplified breast cancers, which represent nearly 30% of all breast cancers, by targeting an important heterodimeric partner of HER2.

Real-Time Monitoring of Rare Circulating Hepatocellular Carcinoma Cells in an Orthotopic Model by In Vivo Flow Cytometry Assesses Resection on Metastasis

Zhi-Chao Fan, Jun Yan, Guang-Da Liu, Xiao-Ying Tan, Xiao-Fu Weng, Wei-Zhong Wu, Jian Zhou, and Xun-Bin Wei

Precise: In vivo flow cytometry may offer a breakthrough technology to elucidate mechanisms of hematogenous metastasis and to monitor the efficacy of cancer therapy.

ABOUT THE COVER

Interleukin-17 (IL-17) is a key proinflammatory cytokine involved in many inflammatory and autoimmune diseases. Mice with conditional knockout of PTEN tumor suppressor gene developed invasive prostate adenocarcinomas at ages of 9 to 30 weeks. When IL-17 signaling was blocked by knockout IL-17 receptor C (IL-17RC) in the PTEN-null mice, the number and size of prostate tumors were reduced compared to mice that expressed IL-17RC, because IL-17RC knockout reduced cellular proliferation, increased apoptosis, inhibited inflammatory infiltration, and diminished expression of matrix metalloproteinase 7 in the mouse prostates. For details, see article by Zhang and colleagues on page 2589 of this issue.