**ACVR1 Mutations in DIPG: Lessons Learned from FOP**
Kathryn R. Taylor, Maria Vinci, Alex N. Bullock, and Chris Jones

**Modeling Contact Guidance and Invasion by Cancer Cells**
Leonard M. Sander

**Force Engages Vinculin and Promotes Tumor Progression by Enhancing PI3K Activation of Phosphatidylinositol (3,4,5)-Triphosphate**
Matthew G. Rubashkin, Luke Cassereau, Russell Bainer, Christopher C. DuFort, Yoshihiro Yui, Guanqing Ou, Matthew J. Paszek, Michael W. Davidson, Yunn-Yi Chen, and Valerie M. Weaver

**Using High-Throughput Transcriptomic Data for Prognosis: A Critical Overview and Perspectives**
Eytan Domany

**Advanced Magnetic Resonance Imaging of the Physical Processes in Human Glioblastoma**
Jayashree Kalpathy-Cramer, Elizabeth R. Gerstner, Kyrre E. Emblem, Ovidiu C. Andronesi, and Bruce Rosen

**Therapies with Diverse Mechanisms of Action Kill Cells by a Similar Exponential Process in Advanced Cancers**
Krastan B. Blagoev, Julia Wilkerson, Wilfred D. Stein, James Yang, Susan E. Bates, and Tito Fojo

**Resistance to Chemotherapy: Patient Variability and Cellular Heterogeneity**
David A. Kessler, Robert H. Austin, and Herbert Levine

**Mouse Models of Human Cancer**
Barbara C. Böck, Ulrike Stein, Clemens A. Schmitt, and Hellmut G. Augustin

**Kinase Domain Activation of FGFR2 Yields High-Grade Lung Adenocarcinoma Sensitive to a Pan-FGFR Inhibitor in a Mouse Model of NSCLC**

**Précis:** In developing a unique mouse model of lung adenocarcinoma, this study may improve what have been limited opportunities for preclinical drug discovery and development in this setting.
INTEGRATED SYSTEMS AND TECHNOLOGIES

4685  Polarization-Sensitive Multimodal Imaging for Detecting Breast Cancer
       Rakesh Patel, Ashraf Khan, Robert Quinlan, and Anna N. Yaroslavsky
       Précis: This study describes a novel noninvasive imaging method that allows for rapid and accurate intraoperative detection of breast cancer margins.

4694  A Search for Novel Cancer/Testis Antigens in Lung Cancer Identifies VCX/Y Genes, Expanding the Repertoire of Potential Immunotherapeutic Targets
       Ayumu Taguchi, Allen D. Taylor, Jaime Rodriguez, Muğe Celiktas, Hui Liu, Xiaotu Ma, Qing Zhang, Chee-Hong Wong, Alice Chin, Luc Girard, Carmen Behrens, Wan L. Lam, Stephen Lam, John D. Minna, Ignacio I. Wistuba, and Samir M. Hanash
       Précis: These results offer preclinical proof-of-concept for an Hsp70 regulatory complex as an appealing anticancer target for the generalized treatment of human malignancy.

MICROENVIRONMENT AND IMMUNOLOGY

4706  Osteopontin Shapes Immunosuppression in the Metastatic Niche
       Sabina Sangaletti, Claudio Tripodo, Sara Sandri, Ilaria Torselli, Caterina Vitali, Chiara Ratti, Laura Botti, Alessia Burocchi, Rossana Porcasi, Andrea Tomirotti, Mario P. Colombo, and Claudia Chiiodoni
       Précis: Activities of a prometastatic molecule appear to differ to some extent when produced by tumor cells versus host immune cells however, from either source it helps establish local immunosuppression within metastatic sites.

4720  IL-1β-Mediated Repression of microRNA-101 Is Crucial for Inflammation-Promoted Lung Tumorigenesis
       Lin Wang, Ling-Fei Zhang, Jing Wu, Shu-Jun Xu, Yang-Yang Xu, Dangsheng Li, Jia-Tao Lou, and Mo-Fang Liu
       Précis: microRNA-101 provides a molecular connection between pathogenic inflammation and lung tumorigenesis by regulating Lin28B, an oncogenic RNA-binding protein with pleiotropic roles in cancer including stem-like cell function.

MOLECULAR AND CELLULAR PATHOBIOLOGY

4731  Hsp70–Bag3 Interactions Regulate Cancer-Related Signaling Networks
       Précis: These results confirm the suspicion that prospects for effective immunotherapy are far more likely to emerge from targeting multiple tumor antigens than single tumor antigens.

4741  NACK Is an Integral Component of the Notch Transcriptional Activation Complex and Is Critical for Development and Tumorigenesis
       Kelly L. Weaver, Marie-Clotilde Alves-Guerra, Ke Jin, Zhiqiang Wang, Xiaoqing Han, Prathibba Ranganathan, Xiaoxia Zhu, Thiafo DaSilva, Wei Liu, Francesca Ratti, Renee M. Demarest, Cristos Tzimas, Meghan Rice, Rodrigo Vasquez-Del Carpio, Nadia Dahmane, David J. Robbins, and Anthony J. Capobianco
       Précis: This study illuminates a novel critical part of the Notch receptor signaling pathway, which has emerged as an important driver of a variety of aggressive human cancers.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4751  Antitumor Effects in Hepatocarcinoma of Isoform-Selective Inhibition of HDAC2
       Yun-Han Lee, Daekwan Seo, Kyung-Ju Choi, Jesper B. Andersen, Min-Ah Won, Mitsuteru Kitade, Luis E. Gómez-Quiroz, Adam D. Judge, Jens U. Marquardt, Chiara Raggi, Elizabeth A. Conner, Ian MacLachlan, Valentina M. Factor, and Snorri S. Thorgeirsson
       Précis: Systemic inactivation of a disease-specific HDAC isoform can achieve therapeutic efficacy, as shown by this preclinical proof-of-concept study for treatment of liver cancer.

4762  Combined SFK/mTOR Inhibition Prevents Rapamycin-Induced Feedback Activation of AKT and Elicits Efficient Tumor Regression
       Jennifer L. Yori, Kristen L. Lozada, Darcie D. Seachrist, Jonathan D. Mosley, Fadi W. Abdul-Karim, Christine N. Booth, Chris A. Flask, and Ruth A. Keri
       Précis: Results from this combination therapy study may help improve the mainly inefficacious effects of mTOR inhibitors in clinical trials, addressing the weaknesses of an erstwhile general approach to cancer cell eradication.
Immediate Utility of Two Approved Agents to Target Both the Metabolic Mevalonate Pathway and Its Restorative Feedback Loop
Aleksandra Pandzla, Peter J. Mullen, Manpreet Kalkat, Rosemary Yu, Janice T. Pong, Zhichua Li, Suzanne Trudel, Karl S. Lang, Mark D. Minden, Aaron D. Schimmer, and Linda Z. Penn

Precis: 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

Precis: 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

Precis: 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, Jezabel Rodriguez-Blanco, Brian Hang, Darren Orton, Lu Han, Baolin Wang, Anthony J. Capobianco, Ethan Lee, and David J. Robbins

Precis: An FDA-approved pinworm drug with potent activity as a casein kinase-1a 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-Kuan Chen, Aysegul A. Sahin, Anil Sood, Gordon B. Mills, Dihua Yu, Gabriel N. Hortobagyi, and Mien-Chie Hung

Precis: 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

Precis: 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. Cabeceras, Mozdeh Mahdavi, Tony Gutscner, Giannicola Genovese, Guocan Wang, Zhuangna Fang, James M. Tepper, Katherine Stemke-Hale, Kenneth Y. Tsai, Michael A. Davies, Gordon B. Mills, and Lynda Chin

Precis: 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.

Chromosomal Instability Selects Gene Copy-Number Variants Encoding Core Regulators of Proliferation in ER- Breast Cancer
David Endesfelder, Rebecca A. Burrell, Nnennaya Kanu, Nicholas McGranahan, Mike Howell, Peter J. Parker, Julian Downward, Charles Swanton, and Maik Kschischo

Precis: Chromosomal instability, a hallmark of cancer cells, permits a selection for gene copy number alterations in core regulators of proliferation that have prognostic value.
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. Shiuh, 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 Kohn
CORRECTIONS

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

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.