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Precis: These findings identify an important new candidate biomarker in renal cell carcinoma that functions in tumor suppression as a key negative modifier of AKT signaling, with potentially broader implications in human cancer.
Notch1-Induced Brain Tumor Models
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Précis: This study is the first to clearly
demonstrate the oncogenic potential of activated
Notch1 and in doing so establishes a novel mouse
model of medulloblastoma.

Survivin-3B Potentiates Immune
Escape in Cancer but Also Inhibits the
Toxicity of Cancer Chemotherapy
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Précis: Cancer-specific alternate splicing that
occurs in the cell death inhibitor survivin
generates a potent mediator of resistance against
immune-mediated or chemotherapeutic killing.

miR-205 Targets PTEN and PHLPP2 to
Augment AKT Signaling and Drive
Malignant Phenotypes in Non–Small
Cell Lung Cancer
Junchao Cai, Lishan Fang, Yongbo Huang,
Rong Li, Jie Yuan, Yi Yang, Xun Zhu,
Baixue Chen, Jueheng Wu, and Mengfeng Li
Précis: These results reveal how AKT becomes
activated in lung adenocarcinoma, identifying a
pivotal role for an oncomir of emerging
importance in the development and progression of
this widespread disease.

FOXL1, a Novel Candidate Tumor
Suppressor, Inhibits Tumor
Aggressiveness and Predicts Outcome
in Human Pancreatic Cancer
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B. Michael Ghadimi, Thomas Ried,
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Précis: FOX transcription factors continue to emerge as
central determinants of cancer pathophysiology and patient outcomes in many
deadly human solid tumors, illustrated in this
study of FOXL1 in pancreatic cancer.

PTK6 Activation at the Membrane
Regulates Epithelial–Mesenchymal
Transition in Prostate Cancer
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André Kajdacsy-Balla, and Angela L. Tyner
Précis: Membrane relocalization and activation
of the nonreceptor tyrosine kinase PTK6 serves as
a novel marker for prostate cancer staging and
prognosis, also offering potential therapeutic
implications for treatment of prostate cancer.

HOXB13 Mediates Tamoxifen
Resistance and Invasiveness in Human
Breast Cancer by Suppressing ERα and
Inducing IL-6 Expression
Nilay Shah, Kideok Jin, Leigh-Ann Cruz,
Sunju Park, Helen Sadik, Soonweng Cho,
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Harikrishna Nakshatri, Rajnish Gupta,
Howard Y. Chang, Zhe Zhang,
Ashley Cimino-Mathews, Leslie Cope,
Christopher Umbricht, and Saraswati Sukumar
Précis: These results establish a function for the
homeodomain transcription factor HOXB13 in the
emergence of tamoxifen resistance in breast
cancer through direct blockade of ERα and
upregulation of the IL-6 pathway.

Inhibition of AMPK and Krebs Cycle
Gene Expression Drives Metabolic
Remodeling of Pten-Deficient
Preneoplastic Thyroid Cells
Valeria G. Antico Arciuch, Marika A. Russo,
Kristy S. Kang, and Antonio Di Cristofano
Précis: This study describes a novel mechanism of
glycolytic upregulation that is distinct from the
Warburg effect and mediated by PKB-dependent
inactivation of the core metabolic kinase AMPK,
with potentially great impact on understanding a
central metabolic question in cancer.
PREVENTION AND EPIDEMIOLOGY

5473 Chemopreventive Activity of Plant Flavonoid Isorhamnetin in Colorectal Cancer Is Mediated by Oncogenic Src and β-Catenin Shakir M. Saud, Matthew R. Young, Yaya L. Jones-Hall, Lilia Ileva, Moses O. Evbuomwan, Jennifer Wise, Nancy H. Colburn, Young S. Kim, and Gerd Bobe Pécis: This study advances mechanistic understanding for the anticancer properties of a natural flavonol that can prevent tumorigenesis, reverse EMT, and block metastasis with limited toxicity in various types of cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY


5497 Werner Syndrome Helicase Has a Critical Role in DNA Damage Responses in the Absence of a Functional Fanconi Anemia Pathway Monika Aggarwal, Taraswi Banerjee, Joshua A. Sommers, Chiara Iannascoli, Pietro Pichierri, Robert H. Shoemaker, and Robert M. Brosh, Jr. Pécis: These findings advance our understanding of cellular resistance to a DNA crosslinking agent used to combat cancer, implicating the WRN helicase as a target for inhibition in cells defective in the Fanconi anemia pathway of DNA repair targeted by certain chemotherapy strategies.

5508 A Synthetic Lethality–Based Strategy to Treat Cancers Harboring a Genetic Deficiency in the Chromatin Remodeling Factor BRG1 Takahiro Oike, Hideaki Ogiwara, Yuichi Tominaga, Kentaro Ito, Osamu Ando, Koji Tsuta, Tatsuji Mizukami, Yoko Shimada, Hisanori Isomura, Mayumi Komachi, Koh Furuta, Shun-Ichi Watanabe, Takashi Nakano, Jun Yokota, and Takashi Kohno Pécis: These results offer a rationale for an epigenetic-based treatment of many lung cancers and other common cancers lacking known therapeutic gene mutations, providing a broad catchment strategy for treatment.

5519 AC1MMYR2, an Inhibitor of Dicer-Mediated Biogenesis of Oncomir miR-21, Reverses Epithelial–Mesenchymal Transition and Suppresses Tumor Growth and Progression Zhendong Shi, Junxia Zhang, Xiaomin Qian, Lei Han, Kailiang Zhang, Lu Yue Chen, Jilong Liu, Yu Ren, Ming Yang, Anling Zhang, Pei Yu Pu, and Chunseng Kang Pécis: This study offers a novel, high-throughput method to screen for small-molecule inhibitors of microRNA maturation and presents an inhibitor of oncomir miR-21 maturation as a candidate antitumor drug.

5532 KEAP1-Dependent Synthetic Lethality Induced by AKT and TXNRD1 Inhibitors in Lung Cancer Bingbing Dai, Suk-Young Yoo, Geoffrey Bartholomeusz, Ryan A. Graham, Mourad Majidi, Shaoyu Yan, Jieru Meng, Lin Ji, Kevin Coombs, John D. Minna, Bingliang Fang, and Jack A. Roth Pécis: This study shows how the Nrf2 cellular antioxidant system of great current interest can be harnessed with Akt inhibitors to attack lung cancer more effectively.

TUMOR AND STEM CELL BIOLOGY

5544 SOX2 Expression Associates with Stem Cell State in Human Ovarian Carcinoma Petra M. Bareiss, Anna Paczulla, Hui Wang, Rebekka Schairer, Stefan Wiehr, Ursula Kohlhofer, Oliver C. Rothfuss, Anna Fischer, Sven Perner, Annette Staehler, Diethelm Wallwiener, Falko Fend, Tanja Fehm, Bernd Pichler, Lothar Kan, Leticia Quintanilla-Martinez, Klaus Schulze-Osthoff, Frank Essmann, and Claudia Lengerke Pécis: The embryonic protein SOX2, which serves as a cancer stem cell marker in a variety of cancers, is shown here to induce the tumorigenic capacity of serous ovarian carcinoma cells.

5556 Hbo1 Is a Cyclin E/CDK2 Substrate That Enriches Breast Cancer Stem-like Cells MyLinh T. Duong, Said Akli, Sira Macalou, Anna Biernacka, Bisrat G. Debeb, Min Yi, Kelly K. Hunt, and Khandan Keyomarsi Pécis: The increased oncogenic potency of cyclin E proteolytic cleavage products, which accumulate in some breast cancers, relates to their ability to promote EMT and cancer stem-like properties, the mechanistic aspects of which have immediate therapeutic implications.
MUC1 Is a Potential Target for the Treatment of Acute Myeloid Leukemia Stem Cells
Dina Stroopinsky, Jacalyn Rosenblatt, Keisuke Ito, Heidi Mills, Li Yin, Hasan Rajabi, Baldev Vasir, Turner Kufe, Katarina Luptakova, Jon Arnason, Caterina Nardella, James D. Levine, Robin M. Joyce, Ilene Galinsky, Yoram Reiter, Richard M. Stone, Pier Paolo Pandolfi, Donald Kufe, and David Avigan

Précis: A mucin gene widely upregulated in solid cancers and studied as an immunotherapeutic target is reported here to serve as a leukemia stem cell marker, broadening interest in its potential uses to better define or eradicate malignancy.

C1GALT1 Enhances Proliferation of Hepatocellular Carcinoma Cells via Modulating MET Glycosylation and Dimerization
Yao-Ming Wu, Chiung-Hui Liu, Miao-Juei Huang, Hong-Shiee Lai, Po-Huang Lee, Rey-Heng Hu, and Min-Chuan Huang

Précis: These findings offer evidence in support of an O-glycosyl transferase as an appealing therapeutic target to develop for treatment of liver cancer.

Distinct FAK Activities Determine Progenitor and Mammary Stem Cell Characteristics
Ming Liao, Xiaofeng Zhao, Song Chen, Suling Liu, Max S. Whia, and Jun-Lin Guan

Précis: These findings define distinct kinase-dependent and kinase-independent activities of the FAK kinase that permit therapeutic strategies to address cancer heterogeneity more effectively, a major challenge for molecular targeted therapeutics generally.

Correction: Cancer Angiogenesis Induced by Kaposi’s Sarcoma-Associated Herpesvirus Is Mediated by EZH2

Correction: Emil Frei III, MD: In Memoriam (1924–2013)

ABOUT THE COVER
The tumor microenvironment contains numerous cellular elements, such as cancer-associated fibroblasts (CAF) and activated myofibroblasts that participate in fibrovascular, vascular, and chemo/cytokine support of tumors. Using bone marrow transplant recipient mice harboring CD44 knockout (KO) mesenchymal stem cells (MSC), the precursor population for CAFs and myofibroblasts, Spaeth and colleagues observed the inability of engrafted CD44-KO stromal cells to provide tumor support, to generate vascular support, and importantly, to transition from the benign MSC phenotype to the tumor-supportive aggressive myofibroblast phenotype. The spectrally unmixed image displays smooth muscle actin + CAFs and myofibroblasts (red) from bone marrow derived CD44-KO (green) MSC in the tumor microenvironment. For details, see article by Spaeth and colleagues on page 5347.