Contents

BREAKING ADVANCES

5299 Highlights from Recent Cancer Literature

REVIEWS

5301 The p90 RSK Family Members: Common Functions and Isoform Specificity
Romain Lara, Michael J. Seckl, and Olivier E. Pardo

5309 mRNA Splicing Variants: Exploiting Modularity to Outwit Cancer Therapy
Scott M. Dehm

PERSPECTIVE

5315 Patient-Derived Tumor Xenografts: Transforming Clinical Samples into Mouse Models
Despina Siolas and Gregory J. Hannon

PRIORITY REPORT

5320 Mammary Tumor Formation and Metastasis Evoked by a HER2 Splice Variant
Abdullah Alajati, Nina Sausgruber, Nicola Aceto, Stephan Duss, Sophie Sarret, Hans Voshol, Debora Bonenfant, and Mohamed Bentires-Alj

5328 EPR Oxygen Images Predict Tumor Control by a 50% Tumor Control Radiation Dose
Martyna Elas, Jessica M. Magwood, Brandi Butler, Chanel Li, Rona Wardak, Rebekah DeVries, Eugene D. Barth, Boris Epel, Samuel Rubinstein, Charles A. Pelizzari, Ralph R. Weichselbaum, and Howard J. Halpern

CLINICAL STUDIES

5328 EPR Oxygen Images Predict Tumor Control by a 50% Tumor Control Radiation Dose
Martyna Elas, Jessica M. Magwood, Brandi Butler, Chanel Li, Rona Wardak, Rebekah DeVries, Eugene D. Barth, Boris Epel, Samuel Rubinstein, Charles A. Pelizzari, Ralph R. Weichselbaum, and Howard J. Halpern

MOLECULAR AND CELLULAR PATHOBIOLOGY

5371 Candidate Tumor Suppressor and pVHL Partner Jade-1 Binds and Inhibits AKT in Renal Cell Carcinoma
Liling Zeng, Ming Bai, Amit K. Mittal, Wassim El-Jouni, Jing Zhou, David M. Cohen, Mina I. Zhou, and Herbert T. Cohen

5360 Fusion-Derived Epithelial Cancer Cells Express Hematopoietic Markers and Contribute to Stem Cell and Migratory Phenotype in Ovarian Carcinoma
Mallika Ramakrishnan, Sandeep R. Mathur, and Asok Mukhopadhyay

5357 Mesenchymal CD44 Expression Contributes to the Acquisition of an Activated Fibroblast Phenotype via TWIST Activation in the Tumor Microenvironment
Erika L. Spaeth, Adam M. Labaff, Bryan P. Toole, Ann Klopp, Michael Andreeff, and Frank C. Marini

5347 Stromally Derived Lysyl Oxidase Promotes Metastasis of Transforming Growth Factor-β–Deficient Mouse Mammary Carcinomas
Michael W. Pickup, Hanane Laklai, Irene Ackerbi, Philip Owens, Agnieszka E. Gorska, Anna Chytir, Mary Aakre, Valerie M. Weaver, and Harold L. Moses

5336 Candidate Tumor Suppressor and pVHL Partner Jade-1 Binds and Inhibits AKT in Renal Cell Carcinoma
Liling Zeng, Ming Bai, Amit K. Mittal, Wassim El-Jouni, Jing Zhou, David M. Cohen, Mina I. Zhou, and Herbert T. Cohen

5336 Microenvironment and Immunology

5336 Stromally Derived Lysyl Oxidase Promotes Metastasis of Transforming Growth Factor-β–Deficient Mouse Mammary Carcinomas
Michael W. Pickup, Hanane Laklai, Irene Ackerbi, Philip Owens, Agnieszka E. Gorska, Anna Chytir, Mary Aakre, Valerie M. Weaver, and Harold L. Moses

5336 Mesenchymal CD44 Expression Contributes to the Acquisition of an Activated Fibroblast Phenotype via TWIST Activation in the Tumor Microenvironment
Erika L. Spaeth, Adam M. Labaff, Bryan P. Toole, Ann Klopp, Michael Andreeff, and Frank C. Marini

5336 EPR Oxygen Images Predict Tumor Control by a 50% Tumor Control Radiation Dose
Martyna Elas, Jessica M. Magwood, Brandi Butler, Chanel Li, Rona Wardak, Rebekah DeVries, Eugene D. Barth, Boris Epel, Samuel Rubinstein, Charles A. Pelizzari, Ralph R. Weichselbaum, and Howard J. Halpern

Precise: These findings suggest that microenvironmental changes triggered by oncogenically transformed epithelial cells can offer important therapeutic targets to inhibit metastasis.

Precise: 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
the Sonic Hedgehog Subgroup of
Human Medulloblastoma
Sivaraman Natarajan, Yaochen Li,
Emily E. Miller, David J. Shih, Michael D. Taylor,
Timothy M. Stearns, Roderick T. Bronson,
Susan L. Ackerman, Jeong K. Yoon, and
Kyuson Yun
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
Frédérique Végran, Romain Mary,
Anne Gibeaud, Céline Mirjolet, Bertrand Collin,
Alexandra Oudot, Céline Charon-Barra,
Laurent Arnould, Sarab Lizard-Nacol, and
Romain Boidot
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
Geng Zhang, Peijun He, Jochen Gaedcke,
B. Michael Ghadimi, Thomas Ried,
Harris G. Yfantis, Dong H. Lee, Nader Hanna,
H. Richard Alexander, and S. Perwez Hussain
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
Yu Zheng, Zebin Wang, Wenjun Bie,
Patrick M. Brauer, Bethany E. Perez White,
Jing Li, Veronique Nogueira,
Pradip Raychaudhuri, Nissim Hay,
Debra A. Tonetti, Virgilia Macias,
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
progression, also offering potential therapeutic
implications for treatment of prostate cancer.

Myoferlin Is a Key Regulator of EGFR
Activity in Breast Cancer
Andrei Turtoi, Arnaud Blomme,
Akeila Bellahcene, Christine Gilles,
Vincent Hennéquère, Paul Peixoto,
Elettia Bianchi, Agnès Noel, Edwin De Pauw,
Eric Lifrance, Philippe Delvenne, and
Vincent Castronovo
Précis: Given the therapeutic significance of EGFR
targeting, this study’s findings highlight a rational
candidate function to target for future drug
development.

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, Soomweng Cho,
Chirayu Pankaj Goswami,
Harikrishna Naikshatri, 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
Prenoeplastic 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 PISK-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, Yawa L. Jones-Hall, Lilia Ileva, Moses O. Evuomwan, Jennifer Wise, Nancy H. Colburn, Young S. Kim, and Gerd Bobe

**Précis:** This study advances mechanistic understanding for the anticancer properties of a natural flavonoid that can prevent tumorigenesis, reverse EMT, and block metastasis with limited toxicity in various types of cancer.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

5485  Novel Small-Molecule Inhibitors of Bcl-XL to Treat Lung Cancer  Dongkyoo Park, Andrew T. Magis, Rui Li, Taofeek K. Owonikoko, Gabriel L. Sica, Shi-Yong Sun, Suresh S. Ramalingam, Fadlo R. Khuri, Walter J. Curran, and Xingming Deng

**Précis:** The new class of Bcl-XL inhibitors identified in this report exhibits distinct specificities and strong potency against lung cancer and acquired radioresistance in this setting.


**Précis:** 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 Ogawa, Yuichi Tominaga, Kentaro Ito, Osamu Ando, Koji Tsuta, Tatsuki Mizzakami, Yoko Shimada, Hisanori Isomura, Mayumi Komachi, Koh Furuta, Shin-Ichi Watanabe, Takashi Nakano, Jun Yokota, and Takashi Kohno

**Précis:** 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.

**TUMOR AND STEM CELL BIOLOGY**

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, Kaiilang Zhang, Luylene Chen, Jilong Liu, Yu Ren, Ming Yang, Anling Zhang, Peiyu Pu, and Chunsheung Kang

**Précis:** 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.

5524  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 Coombes, John D. Minna, Bingliang Fang, and Jack A. Roth

**Précis:** 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.

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 Staebler, Diethelm Wallwiener, Falko Fend, Tanja Fehm, Bernd Pichler, Lothar Kanz, Leticia Quintanilla-Martinez, Klaus Schulze-Osthoff, Frank Essmann, and Claudia Lengerke

**Précis:** The embryonic protein SOX2, which serves as a cancer stem cell marker in a variety of cancers, is shown here to induce the tumor-initiating capacity of serous ovarian carcinoma cells.

5556  Hbo1 Is a Cyclin E/CDK2 Substrate That Enriches Breast Cancer Stem-like Cells  MyLinht T. Duong, Said Akli, Sira Macalou, Anna Biernacka, Bishist G. Debebe, Min Yi, Kelly K. Hunt, and Khandan Keyomarsi

**Précis:** 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. Whicha, 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.