BREAKING ADVANCES

3995 Highlights from Recent Cancer Literature

REVIEWS

3997 The Stress Kinase p38α as a Target for Cancer Therapy
Ana Igea and Angel R. Nebreda

4003 Cell-of-Origin of Cancer versus Cancer Stem Cells: Assays and Interpretations
Kiera Rycaj and Dean G. Tang

4012 The MYC–WDR5 Nexus and Cancer
Lance R. Thomas, Audra M. Foshage, April M. Weissmiller, and William P. Tansey

PERSPECTIVES

4016 Recommendations for Benchmarking Preclinical Studies of Nanomedicines
Charlene M. Davidczyk, Luisa M. Russell, and Peter C. Searson

4021 Inferring the Origin of Metastases from Cancer Phylogenies
Woo Suk Hong, Max Shpak, and Jeffrey P. Townsend

PRIORITY REPORT

4026 Transcriptome Sequencing Reveals PCAT5 as a Novel ERG-Regulated Long Noncoding RNA in Prostate Cancer

Précis: This first transcriptome sequencing of castration-resistant prostate cancer reports the discovery of an long non-coding RNA that may offer a druggable target in ERG+ prostate cancers.

CLINICAL STUDIES

4032 High-Resolution Rapid Diagnostic Imaging of Whole Prostate Biopsies Using Video-Rate Fluorescence Structured Illumination Microscopy
Mei Wang, Hillary Z. Kimbrell, Andrew B. Sholl, David B. Tulman, Katherine N. Elfer, Tyler C. Schlichenmeyer, Benjamin R. Lee, Michelle Lacey, and J. Quincy Brown

Précis: This study describes the utility of a novel microscopic method for high-throughput, nondestructive pathologic imaging and diagnosis of malignant biopsy tissue, with the potential to replace current techniques and assess tissue quality and diagnosis at the point of acquisition.

INTEGRATED SYSTEMS AND TECHNOLOGIES

4042 A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis
Elisabeth Broy, Sandra Rebouissou, Claudine Chaouqui, Andrei Zinovyev, François Radvany, and Laurence Calzone

Précis: This multidisciplinary study explains the basis for mutual exclusivity and co-occurring genetic alterations in bladder cancer through the use of a mathematical model that provides context and temporal orders for these alteration patterns.

4053 Implication of the Autologous Immune System in BCR–ABL Transcript Variations in Chronic Myelogenous Leukemia Patients Treated with Imatinib
Geoffrey D. Clapp, Thomas Lepoutre, Raouf El Cheikh, Samuel Bernard, Jérémie Ruby, Hélène Labussière-Wallet, Franck E. Nicolini, and Doron Levy

Précis: Variations in BCR-ABL transcripts during imatinib therapy may represent a signature of the patient’s individual autologous immune response, as modeled by a mathematical algorithm in this study that may help design patient-specific schedules for TKI combination therapy.
Metastasis Suppressors Regulate the Tumor Microenvironment by Blocking Recruitment of Prometastatic Tumor-Associated Macrophages

Casey Frankenberger, Daniel Rabe, Russell Bainer, Devipriya Sankarasharma, Kiran Chada, Thomas Krausz, Yoav Gilad, Lev Becker, and Marsha Rich Rosner

Précis: These findings suggest that ‘triple-negative’ breast cancer patients may benefit greatly from therapeutics that target tumor-associated macrophages, addressing a clinical need for effective targeted therapies in this setting.

CD38-Expressing Myeloid-Derived Suppressor Cells Promote Tumor Growth in a Murine Model of Esophageal Cancer

Tatiana A. Karakasheva, Todd J. Waldron, Evgeniy Eruslanov, Sang-Bae Kim, Ju-Seog Lee, Shaun O’Brien, Philip D. Hicks, Devraj Basu, Sunil Singhal, Fabio Malavasi, and Anil K. Rustgi

Précis: This report highlights CD38 as a new marker of highly immunosuppressive MDSC as well as a candidate therapeutic target, addressing a long-standing need to more fully define functional biomarkers in this key myeloid cell population mediating immune escape.

Dll4 Blockade in Stromal Cells Mediates Antitumor Effects in Preclinical Models of Ovarian Cancer

Frank Kuhnert, Guoying Chen, Sandra Coetzee, Nithya Thambi, Carlos Hickey, Jing Shan, Pavel Kovalenko, Irene Nogaera-Troise, Eric Smith, Jeanette Fairhurst, Julian Andreev, Jessica R. Kirshner, Nicholas Papadopoulos, and Gavin Thurston

Précis: These findings establish a therapeutic rationale for antibody-based targeting of a Notch ligand in ovarian cancer, as an antiangiogenic strategy that is particularly potent in combination with VEGF blockade.

Anti-CD20 Therapy Acts via FcγRIIIA to Diminish Responsiveness of Human Natural Killer Cells

Cristina Capuano, Maddalena Romanelli, Chiara Pighi, Giuseppe Cimino, Angela Rago, Rosa Molfetta, Rossella Paolini, Angela Santoni, and Ricciarda Galandrini

Précis: These findings define a novel mechanism of immune exhaustion caused by rituximab or related CD20 mAb in human natural killer cells, with potentially negative implications for patients treated with these therapies.

Carbonic Anhydrase Activity Monitored In Vivo by Hyperpolarized 13C-Magnetic Resonance Spectroscopy Demonstrates Its Importance for pH Regulation in Tumors


Précis: An enzyme that is highly elevated in hypoxic conditions and that engenders metastatic progression is found to have a critical role for lowering extracellular pH, with potential implications as a therapeutic target in hypoxic conditions when tumors are typically resistant to therapy.

The miR-146b-3p/PAX8/NIS Regulatory Circuit Modulates the Differentiation Phenotype and Function of Thyroid Cells during Carcinogenesis

Garcilaso Riesco-Eizaguirre, Leon Vert-Lamas, Javier Perales-Patón, Ana Sastre-Perona, Lara P. Fernández, and Pilar Santisteban

Précis: These findings reveal that a microRNA network underlies thyroid cell differentiation and function, with important implications for overcoming treatment-refractory metastatic thyroid cancer.

Hepatocyte Growth Factor/cMET Pathway Activation Enhances Cancer Hallmarks in Adrenocortical Carcinoma


Précis: These findings show that HGF/MET signaling enhances cancer hallmarks in adrenocortical carcinoma, where it may also contribute to drug resistance, with implications for the use of MET inhibitors as a clinical treatment strategy in this disease.

HTLV-1 bZIP Factor RNA and Protein Impart Distinct Functions on T-cell Proliferation and Survival

Yuichi Mitobe, Jun-ichirou Yasunaga, Rie Funuta, and Masao Matsuoka

Précis: This study elucidates a central function in the human cancer virus HTLV-1 that enables it to efficiently promote leukemogenesis.
Akt Kinase-Interacting Protein 1 Signals in Cell Surface Recycling Dynamics

These findings show how cell surface recycling dynamics are controlled by endocytic processes, which account for high surface levels of CXCR4 and CCR7 in chronic B cell tumors, and how the targeted drug ibrutinib impacts this balance in achieving therapeutic responses.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**4164**  
VR23: A Quinoline–Sulfonyl Hybrid Proteasome Inhibitor That Selectively Kills Cancer via Cyclin E–Mediated Centrosome Amplification

Sheetal Pundir, Hai-Yen Vu, V. Raja Solomon, Rebecca McClure, and Hoyun Lee

**Précis:** These results identify a structurally novel proteasome inhibitor with uniquely selective anticancer properties and other desirable features, providing a preclinical proof of concept that encourages further clinical development.

**4176**  
Genome-Wide Identification and Characterization of Novel Factors Conferring Resistance to Topoisomerase II Poisons in Cancer

Ruud H. Wijdeven, Baoxu Pang, Sabina Y. van der Zanden, Xiaohang Qiao, Vincent Blomen, Marlous Hoogstraat, Esther H. Wessels, Lennert Janssen, Lodewyk Wessels, Thijn R. Brummelkamp, and Jacques Neeftjes

**Précis:** These findings describe the characterization of three novel mechanisms underlying resistance to the commonly used anticancer drugs doxorubicin and etoposide, with implications for stratifying cancer patients into the most effective treatment regimens.

**4188**  
Akt Kinase-Interacting Protein 1 Signals through CREB to Drive Diffuse Malignant Mesothelioma

Tadaaki Yamada, Joseph M. Amann, Koji Fukuda, Shinji Takeuchi, Naoya Fujita, Hisanori Uehara, Shotaro Iwakiri, Kazumi Itoi, Konstantin Shilo, Seiji Yano, and David P. Carbone

**Précis:** These findings suggest an important role for the Akt1/CREB axis in the pathogenesis of diffuse malignant mesothelioma, a deadly lung cancer, and also offer a preclinical rationale to target Akt1 in this disease setting.

**4198**  
Feed-Forward Reciprocal Activation of PAFR and STAT3 Regulates Epithelial–Mesenchymal Transition in Non–Small Cell Lung Cancer

Jie Chen, Tian Lan, Weimin Zhang, Lijia Dong, Nan Kang, Shumin Zhang, Ming Fu, Bing Liu, Kangtai Liu, and Qimin Zhan

**Précis:** These results elucidate a powerful mechanism of self-reinforcing malignant character in lung adenocarcinoma, driven by a tripartite G protein-coupled receptor that may offer an appealing therapeutic target.

**TUMOR AND STEM CELL BIOLOGY**

**4224**  
Ceacam1L Modulates STAT3 Signaling to Control the Proliferation of Glioblastoma-Initiating Cells

Sadahiro Kaneko, Yuka Nakatani, Tatsuya Takezaki, Takuichiro Hide, Daisuke Yamashita, Naoki Ohtsu, Takamori Ohnishi, Shunsuke Terasaka, Kiyojiro Houkin, and Toru Kondo

**Précis:** These results identify a role for a proangiogenic immunosuppressive cell adhesion protein in maintaining cancer stem-like cell functions in the most commonly deadly brain tumor.

**4235**  
Colon Cancer Growth and Dissemination Relies upon Thrombin, Stromal PAR-1, and Fibrinogen

Gregory N. Adams, Leah Rosenfeld, Malinda Frederick, Whitney Miller, Dusty Walz, Keith Kombbrick, Kathryn E. McElhinney, Matthew J. Flick, Brett P. Monia, Alexey S. Revenko, and Joseph S. Palumbo

**Précis:** Colon cancers may exhibit a special reliance on hemostatic factors such as thrombin, which appears to act as a multifaceted positive modifier of primary tumor growth, invasion, and metastasis, with immediate therapeutic implications for the clinical exploration of inhibitors of thrombin or thrombin generation in this disease setting.
ABOUT THE COVER

Dll4-expressing endothelial cells activate Notch1 on adjacent ovarian tumor cells. Immunohistochemical staining for active Notch1 (nuclear Notch1 intracellular domain) and the tumor cell marker vimentin demonstrates Notch1 signaling activity in the tumor vasculature (elongated nuclei) and in vimentin-positive, tumor vessel-associated parenchymal cells. This pattern illustrates the important concept of juxtacrine signaling interactions between Dll4 expressed by endothelial cells and adjacent, Notch1-positive ovarian tumor cells. For details, see article by Kuhnert and colleagues on page 4086.