The Stress Kinase p38 as a Target for Cancer Therapy
Ana Igea and Angel R. Nebreda

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

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

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

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

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

High-Resolution Rapid Diagnostic Imaging of Whole Prostate Biopsies Using Video-Rate Fluorescence Structured Illumination Microscopy
Mei Wang, Hillary Z. Kimber, 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.

A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis
Elisabeth Bény, Sandra Rebouissou, Claudine Chaoukiya, Andrei Zinoviyev, François Radvanyi, 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.

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, Jérémy 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.
### MICROENVIRONMENT AND IMMUNOLOGY

**4063** 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.

**4074** 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.

**4086** 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 Noguera-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.

**4097** Anti-CD20 Therapy Acts via FcγRIIIA to Diminish Responsiveness of Human Natural Killer Cells

Cristina Capuano, Maddalena Romanelli, Chiara Pighi, Giuseppe Cinino, 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.

### MOLECULAR AND CELLULAR PATHOBIOLOGY

**4109** 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.

**4119** The miR-146b-3p/PAX8/NIS Regulatory Circuit Modulates the Differentiation Phenotype and Function of Thyroid Cells during Carcinogenesis

Garcilaso Riesco-Eizaguirre, León Wert-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.

**4131** 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.

**4143** 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
4188
Genome-Wide Identification and
4176
VR23: A Quinoline
4164
Enhanced Chemokine Receptor Recycling and
4153
Impaired S1P1 Expression Promote Leukemic
Cell Infiltration of Lymphe Nodes in Chronic
Lymphocytic Leukemia
Laura Patrussi, Nagaja Capitani, Veronica Martini,
Marco Pizzi, Valentina Trimanico, Federica Frezzaio,
Filippo Marino, Gianpietro Semenzato, Livio Trentin,
and Cosima T. Baldari
Précis: These findings show how cell surface recycling
dynamics controlled by endocytotic processes 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 Neefjes
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, Liija 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.

4211
Identification of P450 Oxidoreductase as a
Major Determinant of Sensitivity to Hypoxia-
Activated Prodrugs
Francis W. Hunter, Richard J. Young, Zvi Shalev,
Ravi N. Vellanki, Jingli Wang, Yongchuan Gu,
Naveen Joshi, Sreevalsan Sreebhavan, Ilan Weinreb,
David P. Goldstein, Jason Moffat, Troy Ketela,
Kevin R. Brown, Marianne Koritzinsky,
Benjamin Solomon, Danny Rischin, William R. Wilson,
and Bradly G. Wouters
Précis: This study identifies a factor that appears to be
critical for the response to a class of hypoxia-targeting
drugs, with implications for improving the treatment of
hypoxic solid tumors.

TUMOR AND STEM CELL BIOLOGY

4224
Ceacam1L Modulates STAT3 Signaling to
Control the Proliferation of Glioblastoma-
Initiating Cells
Sadahiro Kaneko, Yuka Nakatani, Tatsuya Takezaki,
Takushi Hiro Hide, Daisuke Yamashita, Naoki Ohtsu,
Takunori Ohnishi, Shunsuke Terasaka,
Kiyoshi 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
death 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 Kombinick,
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.