


BREAKING ADVANCES

- 3995** Highlights from Recent Cancer Literature

REVIEWS

- 3997**  The Stress Kinase p38 α 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. Dawidczyk, 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
Antti Ylipää, Kati Kivinummi, Annika Kohvakka, Matti Annala, Leena Latonen, Mauro Scaravilli, Kimmo Kartasalo, Simo-Pekka Leppänen, Serdar Karakurt, Janne Seppälä, Olli Yli-Harja, Teuvo L.J. Tammela, Wei Zhang, Tapio Visakorpi, and Matti Nykter
- Précis:* This first transcriptome sequencing of castration-resistant prostate cancer reports the discovery of a 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 Remy, Sandra Rebouissou, Claudine Chaouiya, Andrei Zinovyev, 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.
- 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, 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.

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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 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.

4109 Carbonic Anhydrase Activity Monitored *In Vivo* by Hyperpolarized ¹³C-Magnetic Resonance Spectroscopy Demonstrates Its Importance for pH Regulation in Tumors

Ferdia A. Gallagher, Helen Sladen, Mikko I. Kettunen, Eva M. Serrao, Tiago B. Rodrigues, Alan Wright, Andrew B. Gill, Sarah McGuire, Thomas C. Booth, Joan Boren, Alan McIntyre, Jodi L. Miller, Shen-Han Lee, Davina Honess, Sam E. Day, De-En Hu, William J. Howat, Adrian L. Harris, and Kevin M. Brindle

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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

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

Liem M. Phan, Enrique Fuentes-Mattei, Weixin Wu, Guermarie Velazquez-Torres, Kanishka Sircar, Christopher G. Wood, Tao Hai, Camilo Jimenez, Gilbert J. Cote, Levent Ozsari, Marie-Claude Hofmann, Siyuan Zheng, Roeland Verhaak, Lance Pagliaro, Maria Angelica Cortez, Mong-Hong Lee, Sai-Ching J. Yeung, and Mouhammed Amir Habra

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 Furuta, and Masao Matsuoka

Précis: This study elucidates a central function in the human cancer virus HTLV-1 that enables it to efficiently promote leukemogenesis.



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4153 Enhanced Chemokine Receptor Recycling and Impaired S1P1 Expression Promote Leukemic Cell Infiltration of Lymph Nodes in Chronic Lymphocytic Leukemia

Laura Patrussi, Nagaja Capitani, Veronica Martini, Marco Pizzi, Valentina Trimarco, Federica Frezzato, 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 Aki1/CREB axis in the pathogenesis of diffuse malignant mesothelioma, a deadly lung cancer, and also offer a preclinical rationale to target Aki1 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.

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 Bradley 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, Takuichiro Hide, Daisuke Yamashita, Naoki Ohtsu, Takanori Ohnishi, Shunsuke Terasaka, Kiyohiro 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 Rosenfeldt, Malinda Frederick, Whitney Miller, Dusty Waltz, Keith Kombrinck, 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.

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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.

