**BREAKING ADVANCES**

7337  Highlights from Recent Cancer Literature

**REVIEWS**

7339  The Evolution of Endothelial Regulatory Paradigms in Cancer Biology and Vascular Repair
Joseph W. Franses and Elazer R. Edelman

7345  The Pax-5 Gene: A Pluripotent Regulator of B-cell Differentiation and Cancer Disease
Pierre O’Brien, Pier Morin Jr, Rodney J. Ouellette, and Gilles A. Robichaud

**MEETING REPORT**

7351  Targeting PI3K/mTOR Signaling in Cancer
Brooke M. Emerling and Argun Akcakanat

**PRIORITY REPORT**

7360  5-Hydroxymethylcytosine Is Strongly Depleted in Human Cancers but Its Levels Do Not Correlate with IDH1 Mutations
Seung-Gi Jin, Yong Jiang, Runxiang Qiu, Tibor A. Rauch, Yinxheng Wang, Gabriele Schackert, Dietmar Krex, Qiang Lu, and Gerd P. Pfeifer

Précis: This study identifies an intermediate step in the process of DNA demethylation as a new contributor to aberrant cancer epigenomes.

7360  Quantifying the Role of Angiogenesis in Malignant Progression of Gliomas: In Silico Modeling Integrates Imaging and Histology
Kristin R. Swanson, Russell C. Rockne, Jonathan Claridge, Mark A. Chaplain, Ellsworth C. Alvord Jr, and Alexander R.A. Anderson

Précis: This modeling study shows that malignant progression of a tumor does not necessarily rely on changes in either the rate of proliferation or invasion.

7360  Metabolomic Profiling Reveals Potential Markers and Bioprocesses Altered in Bladder Cancer Progression

Précis: Metabolic profiling in bladder cancer reveals candidate biomarkers that may be effective in urine sample analysis, with the potential to offer a simple, cost-effective means of diagnosis and prognosis in this disease.

7360  In Vivo Magnetic Resonance Imaging of the Estrogen Receptor in an Orthotopic Model of Human Breast Cancer
Adi Pais, Chidambaram Gumanathan, Raanan Margalit, Inbal Eti Biton, Ady Yosepovich, David Milstein, and Hadassa Degani

Précis: Findings offer preclinical proof-of-concept for a novel ER-targeting contrast agent that can detect ER-positive tumors in a noninvasive manner in vivo.
A Framework to Select Clinically Relevant Cancer Cell Lines for Investigation by Establishing Their Molecular Similarity with Primary Human Cancers
Garrett M. Dancik, Yuanbin Ru, Charles R. Owens, and Dan Theodorescu

Précis: Unfortunately, experimental findings from established human cancer cell lines often do not translate to clinical settings, but by selecting cell lines that better reflect human pathobiology it may be possible to improve this situation.

MICROENVIRONMENT AND IMMUNOLOGY

Précis: Antibody targeting of cell surface proteoglycans that are widely overexpressed in human tumors offers an appealing general approach for passive immunotherapy in cancer patients.

Peptide-Conjugated PAMAM Dendrimer as a Universal DNA Vaccine Platform to Target Antigen-Presenting Cells
Pirouz Daftarian, Angel E. Kaifer, Wei Li, Bonnie B. Blomberg, Daniela Frasca, Felix Roth, Raquibul Chowdhury, Eric A. Berg, Jordan B. Fishman, Husain A. Al Sayegh, Pat Blackwelder, Luca Inverardi, Victor L. Perez, Vance Lemmon, and Paolo Serafini

Précis: This article describes a new DNA vaccination technology that more efficiently targets dendritic cells in vivo, resulting in the production of high-affinity T cells that can more efficiently reject tumors.

PGE2-Induced CXCL12 Production and CXCR4 Expression Controls the Accumulation of Human MDSCs in Ovarian Cancer Environment
Natasa Obermajer, Ravikumar Muthuswamy, Kunle Odunsi, Robert P. Edwards, and Pawel Kalinski

Précis: This study provides a strong rationale for clinical testing of prostaglandin E2 antagonists, such as COX-2 inhibitors or EP2/EP4 blockers, in treatment of tumor ascites, a deadly feature of certain advanced cancers, including ovarian cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Précis: A targetable cell surface receptor is found to be essential for invasion and metastasis of a deadly type of muscle-derived pediatric tumor, with immediate implications to improve its treatment.
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<td><strong>Lysosomal Transmembrane Protein LAPTM4B Promotes Autophagy and Tolerance to Metabolic Stress in Cancer Cells</strong></td>
<td>Yang Li, Qing Zhang, Ruiyang Tian, Qi Wang, Jean J. Zhao, J. Dirk Iglehart, Zhigang Charles Wang, and Andrea L. Richardson</td>
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<td><strong>p53-Responsive miR-194 Inhibits Thrombospondin-1 and Promotes Angiogenesis in Colon Cancers</strong></td>
<td>Prema Sundaram, Stacy Halline, Lauren M. Smith, Michael Dew, Jamie L. Fox, Dauren Biyashev, Janell M. Schelter, Qihong Huang, Michele A. Cleary, Olga V. Volpert, and Andrei Thomas-Tikhonenko</td>
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<td><strong>Angiopoietin-like Protein 2 Is an Important Facilitator of Inflammatory Carcinogenesis and Metastasis</strong></td>
<td>Jun Aoi, Motoyoshi Endo, Tsuyoshi Kadomatsu, Keishi Miyata, Masahiro Nakano, Haruki Horiguchi, Aki Ogata, Haruki Odagiri, Masato Yano, Kumi Araki, Masatoshi Jinnin, Takaaki Ito, Satoshi Hirakawa, Hironobu Ihn, and Yuichi Oike</td>
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<td><strong>Cyclin D3 Compensates for the Loss of Cyclin D1 during ErbB2-Induced Mammary Tumor Initiation and Progression</strong></td>
<td>Qian Zhang, Kazushito Sakamoto, Chenghao Liu, Aleata A. Triplett, Wan-chi Lin, Hallgeir Rui, and Kay-Uwe Wagner</td>
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<td><strong>Androgen Receptor and Nutrient Signaling Pathways Coordinate the Demand for Increased Amino Acid Transport during Prostate Cancer Progression</strong></td>
<td>Qian Wang, Charles G. Bailey, Cynthia Ng, Jessamy Tiffen, Amora Thoeng, Vineet Minhas, Melanie L. Lehman, Stephen C. Hendy, Grant Buchanan, Colleen C. Nelson, John E.J. Rasko, and Jeff Holst</td>
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<td><strong>Autophagy Enhanced by Microtubule- and Mitochondrion-Associated MAP1S Suppresses Genome Instability and Hepatocarcinogenesis</strong></td>
<td>Rui Xie, Fen Wang, Wallace L. McKeenhan, and Leyuan Liu</td>
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<td><strong>Hepatitis B Virus Large Surface Antigen Promotes Liver Carcinogenesis by Activating the Src/P3K/Akt Pathway</strong></td>
<td>Haiou Liu, Jieje Xu, Lei Zhou, Xiaojing Yun, Lin Chen, Shanshan Wang, Linlin Sun, Yumei Wen, and Jianxin Gu</td>
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<td><strong>Phosphorylation of Carbonic Anhydrase IX Controls Its Ability to Mediate Extracellular Acidification in Hypoxic Tumors</strong></td>
<td>Peter Ditte, Franck Dequiedt, Eliska Svastova, Albeta Halikova, Anna Ohradanova-Repic, Miriam Zatovicova, Lucia Csaderova, Juraj Kopacek, Claudiu T. Supuran, Silvia Pastorekova, and Jaromir Pastorek</td>
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PREVENTION AND EPIDEMIOLOGY

7568 Genome-Wide High-Density SNP Linkage Search for Glioma Susceptibility Loci: Results from the Gliogene Consortium

Précis: Linkage analysis of families with 2 or more cases of glioma identifies loci linked to glioma susceptibility, suggesting an inherited predisposition to development of this deadly cancer.

7569 Variations in HSPA1B at 6p21.3 Are Associated with Lung Cancer Risk and Prognosis in Chinese Populations
Huan Guo, Qifei Deng, Chen Wu, Lingmin Hu, Sheng Wei, Ping Xu, Dan Kuang, Li Liu, Zhibin Hu, Xiaoping Miao, Hongbing Shen, Dongxin Lin, and Tangchun Wu

Précis: Functional variants in a human member of the Hsp70 gene family are found to be significantly associated with lung cancer risk and patient survival, possibly offering new clinical biomarkers for risk and prognosis.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

7576 Glioblastoma-Derived Epidermal Growth Factor Receptor Carboxyl-Terminal Deletion Mutants Are Transforming and Are Sensitive to EGFR-Directed Therapies
Jeonghee Cho, Sandra Pastorino, Qing Zeng, Xiaoyin Xu, William Johnson, Scott Vandenberg, Roel Verhaak, Andrew D. Cherniack, Hideo Watanabe, Amit Dutt, Jihyun Kwon, Ying S. Chao, Robert C. Onofrio, Derek Chiang, Yuki Yuza, Santosh Kesari, and Matthew Meyerson

Précis: Genomic and functional analyses of primary gliomas reveal intragenic genomic deletions within the EGFR C-terminal domain that render the receptor oncogenic in vitro and in vivo.

7579 Dual IGF-1R/InsR Inhibitor BMS-754807 Synergizes with Hormonal Agents in Treatment of Estrogen-Dependent Breast Cancer
Xiaonian Hou, Fei Huang, Luciana F. Macedo, Sean C. Harrington, Karen A. Reeves, Ann Greer, Friedrich Graf Finckenstein, Angela Brodie, Marco M. Gottardis, Joan M. Carboni, and Paul Halaska

Précis: Findings offer preclinical proof-of-concept for a powerful new combinatorial approach to improve the eradication of estrogen-dependent breast cancers.

7580 miR-221 Silencing Blocks Hepatocellular Carcinoma and Promotes Survival

Précis: In hepatocellular carcinomas with typically poor prognosis, antisense miR-221 treatments may be highly effective in blocking tumor proliferation.

7581 miR-221 Silencing Blocks Hepatocellular Carcinoma and Promotes Survival

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7582 Chemotherapeutic Properties of Phospho-Nonsteroidal Anti-Inflammatory Drugs, a New Class of Anticancer Compounds
Liqun Huang, Gerardo G. Mackenzie, Yu Sun, Nengtai Ouyang, Gang Xie, Kvetoslava Vrankova, Despina Komninou, and Basil Rigas

Précis: This important study addresses the quandary posed by NSAIDs, which exert useful anti-inflammatory effects but present safety and efficacy concerns that raise questions about their use in cancer prevention and treatment.

7583 Wnt Inhibitor Screen Reveals Iron Dependence of β-Catenin Signaling in Cancers

Précis: In identifying a new class of compounds suitable for development as inhibitors of Wnt-driven cancers, this study led to the important discovery of a fundamental requirement for iron that might be immediately clinically exploitable.
SMAC Mimetic (JP1201) Sensitizes Non–Small Cell Lung Cancers to Multiple Chemotherapy Agents in an IAP-Dependent but TNF-α–Independent Manner
Rachel M. Greer, Michael Peyton, Jill E. Larsen, Luc Girard, Yang Xie, Adi F. Gazdar, Patrick Harran, Lai Wang, Rolf A. Brekken, Xiaodong Wang, and John D. Minna

Précis: Chemical mimetics of the proapoptotic molecule SMAC may be useful to broadly sensitize chemoresistant cancers to clinically relevant concentrations of various cytotoxic drugs, addressing an urgent need in oncology.

Thrombospondin-1 Triggers Cell Migration and Development of Advanced Prostate Tumors
Virginie Firlej, Jacques R.R. Mathieu, Christele Gilbert, Loïc Lemonnier, Jessica Naklle, Catherine Gallou-Kabani, Basma Guarmit, Aurèle Morin, Natalia Prevarskaya, Nicolas Barry Delongchamps, and Florence Cabon

Précis: An extracellular protein known to be anti-angiogenic was found to stimulate invasion in prostate cancers, suggesting that disruption of this protein might actually confer therapeutic benefits.

Sorcin Induces a Drug-Resistant Phenotype in Human Colorectal Cancer by Modulating Ca2+ Homeostasis
Francesca Maddalena, Gabriella Laudiero, Annamaria Piscazzi, Agnese Secondo, Antonella Scorziello, Valentina Lombardi, Danilo Swann Matassa, Alberto Fersini, Vincenzo Neri, Franca Esposito, and Matteo Landriscina

Précis: Findings elucidate what appears to be a broadly active mechanism of multidrug resistance in human colorectal cancers, potentially responsible for much of the mortality in this common cancer in developed countries.

TUMOR AND STEM CELL BIOLOGY

Targets of the Tumor Suppressor miR-200 in Regulation of the Epithelial–Mesenchymal Transition in Cancer
Mark J. Schliekelman, Don L. Gibbons, Vitor M. Faca, Chad J. Creighton, Zain H. Rizvi, Qing Zhang, Chee-Hong Wong, Hong Wang, Christin Ungewiss, Young-Ho Ahn, Dong-Hoon Shin, Jonathan M. Kurie, and Samir M. Hanash

Précis: Findings offer insights into how a family of tumor suppressive microRNAs restricts metastatic progression, identifying key roles for a TGF-β protein network and extracellular cell adhesion molecules and proteases in the tumor microenvironment.

Selectin Ligand Sialyl-Lewis x Antigen Drives Metastasis of Hormone-Dependent Breast Cancers
Sylvain Julien, Aleksandar Ivetic, Anita Grigoriadis, Ding QiZe, Brian Burford, Daisy Sproviero, Gianfranco Picco, Cheryl Gillett, Suzanne L. Papp, Lana Schaffer, Andrew Tutt, Joyce Taylor-Papadimitriou, Sarah E. Pinder, and Joy M. Burchell

Précis: Findings identify a cell surface glycosylation marker on breast cancer cells that is associated with metastasis to the bone, offering insights into the context of its activity.

GLIPR1 Suppresses Prostate Cancer Development through Targeted Oncoprotein Destruction
Likun Li, Chengzheng Ren, Guang Yang, Elmoataz Abdel Fattah, Alexei A. Goltsov, Soo Mi Kim, Ju-Seog Lee, Sanghee Park, Francesco J. Demayo, Michael M. Ittmann, Patricia Troncoso, and Timothy C. Thompson

Précis: This study offers important new insights into how the c-myc gene becomes deregulated in human cancers, addressing long-standing questions of general interest to the field and suggesting new ideas on how to attack this pivotal molecule.

Aptosis Inhibitor ARC Promotes Prostate Cancer Development through Targeted Oncoprotein Destruction
Likun Li, Chengzheng Ren, Guang Yang, Elmoataz Abdel Fattah, Alexei A. Goltsov, Soo Mi Kim, Ju-Seog Lee, Sanghee Park, Francesco J. Demayo, Michael M. Ittmann, Patricia Troncoso, and Timothy C. Thompson

Précis: This study reveals multiple pathobiologic roles for the apoptosis suppressor ARC in driving carcinogenesis and chemoresistance.

LETTERS TO THE EDITOR

STK33 Kinase Is Not Essential in KRAS-Dependent Cells–Letter
Stefan Fröhling and Claudia Scholl

STK33 Kinase Is Not Essential in KRAS-Dependent Cells–Response
Isabelle Dussault, Josette Carnahan, Carol Babij, Yihong Zhang, Vivienne J. Watson, Kim Quon, and Paul D. Kassner

CORRECTION

Correction: Definition of a FoxA1 Cistrome That Is Crucial for G1 to S-Phase Cell-Cycle Transit in Castration-Resistant Prostate Cancer
ABOUT THE COVER

Chronic inflammation plays important roles at different stages of cancer development, including carcinogenesis, tumor invasion, and metastasis. In this study, expression of angiopoietin-like protein 2 (Angptl2), recently identified as a chronic inflammation mediator in skin tissues, is highly correlated with the frequency of carcinogenesis in a chemically induced skin squamous cell carcinoma (SCC) mouse model. Furthermore, expression of Angptl2 in tumor cells promotes not only tumor angiogenesis and lymphangiogenesis, but also the acquisition of mesenchymal invasive characteristics in tumor cells through activation of TGF-β/Smad signaling, resulting in worse outcomes. This image represents a significantly increased tumor angiogenesis in SCC of Angptl2 transgenic (K14-Angptl2) mice. For details, see the article by Aoi and colleagues on page 7502 of this issue.