**BREAKING ADVANCES**

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Highlights from Recent Cancer Literature

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

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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

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

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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, Yinsheng Wang, Gabriele Schackert, Dietmar Krex, and Qiang Lu

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

7366  
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

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

7376  
Metabolomic Profiling Reveals Potential Markers and Bioprocesses Altered in Bladder Cancer Progression  

**Precis:** 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.

7387  
In Vivo Magnetic Resonance Imaging of the Estrogen Receptor in an Orthotopic Model of Human Breast Cancer  
Adi Pais, Chidambaram Gunanathan, Raanan Margalit, Inbal Eti Biton, Ady Yosepovich, David Milstein, and Hadassa Degani

**Precis:** 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.

Functional Characterization of an scFv-Fc Antibody that Immunotherapeutically Targets the Common Cancer Cell Surface Proteoglycan CSPG4
Xinhui Wang, Akihiro Katayama, Yangyang Wang, Ling Yu, Elvira Favoino, Koichi Sakakura, Alessandra Favole, Takahiro Tsukikawa, Susan Silver, Simon C. Watkins, Yoshiro Kageshita, and Soldano Ferrone

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.

Smad7 Expression in T cells Prevents Colitis-Associated Cancer
Angelamaria Rizzo, Maximilian J. Waldner, Carmine Stolfi, Massimiliano Sarra, Daniele Fina, Christoph Becker, Markus F. Neurath, Thomas T. Macdonald, Francesco Pallone, Giovanni Monteleone, and Massimo C. Fantini

Précis: This study illustrates that chronic inflammation in colitis does not necessarily heighten risks of colorectal tumorigenesis, based on epigenetic differences in the immune microenvironment that dictate whether colitis-associated inflammation promotes or retards tumor development.

Hypoxia Induces Escape from Innate Immunity in Cancer Cells via Increased Expression of ADAM10: Role of Nitric Oxide
Ivraym B. Barsoum, Thomas K. Hamilton, Xin Li, Tiziana Cotechini, Allen A. Miles, D. Robert Siemens, and Charles H. Graham

Précis: Nitric oxide can block hypoxia-mediated evasion from innate immunity, suggesting the immediate clinical exploration of nitric oxide mimetics like nitroglycerin for cancer treatment.

Dendritic Cell Internalization of α-Galactosylceramide from CD8 T Cells Induces Potent Antitumor CD8 T-cell Responses
Dong Hoon Choi, Kwang Soon Kim, Se Hwan Yang, Do Hyun Chung, Boyeong Song, Jonathan Sprent, Jae Ho Cho, and Young Chul Sung

Précis: This study reports a strategy that might generally improve any adoptive T-cell immunotherapy, based on treatment of the T cells with an immune stimulatory lipid prior to transfer into 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, Hussain A. Al Sayegh, Pat Blackwelder, Luca Inverardi, Victor L. Perez, Vane 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
Nataša 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.

PAX3-FOXO1 Induces Cannabinoid Receptor 1 to Enhance Cell Invasion and Metastasis
Amy D. Marshall, Irina Lagutina, and Gerard C. Grosveld

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.
Lysosomal Transmembrane Protein LAPTM4B Promotes Autophagy and Tolerance to Metabolic Stress in Cancer Cells
Yang Li, Qing Zhang, Ruiyang Tian, Qi Wang, Jean J. Zhao, J. Dirk Iglehart, Zhigang Charles Wang, and Andrea L. Richardson

**Précis:** Upregulation of a lysosomal protein is implicated in chemoresistance and breast cancer functions by promoting autophagy and inhibiting lysosome-mediated cell death.

p53-Responsive miR-194 Inhibits Thrombospondin-1 and Promotes Angiogenesis in Colon Cancers
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

**Précis:** Studies of a p53 responding miRNA suggest mechanistic insights into how angiogenesis is regulated during colon cancer development.

Angiopoietin-like Protein 2 Is an Important Facilitator of Inflammatory Carcinogenesis and Metastasis
Jun Aoi, Motoyoishi Endo, Tsuyoshi Kadomatsu, Keishi Miyata, Masahiro Nakano, Haruki Horiguchi, Aki Ogata, Haruki Odagiri, Masato Yano, Kimi Araki, Masatoshi Jinnin, Takaaki Ito, Satoshi Hirakawa, Hironobu Ihn, and Yuichi Oike

**Précis:** An angiogenesis-related factor recently linked to chronic inflammation is a key driver of tumor initiation and progression, with implications for a tractable new therapeutic approach to treat or prevent inflammation-associated cancers.

Cyclin D3 Compensates for the Loss of Cyclin D1 during ErbB2-Induced Mammary Tumor Initiation and Progression
Qian Zhang, Kazuhito Sakamoto, Chenghao Liu, Aleata A. Triplett, Wan-chi Lin, Hallgerd Rui, and Kay-Uwe Wagner

**Précis:** Broad targeting of cyclin D functions may be essential for effective treatment of ErbB2-induced breast cancers due to functional cross compensation between cyclin D isoforms.

Androgen Receptor and Nutrient Signaling Pathways Coordinate the Demand for Increased Amino Acid Transport during Prostate Cancer Progression
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

**Précis:** Androgen signaling and amino acid stress pathways work together to maintain adequate levels of essential amino acids vital for mTOR activation and prostate cancer outgrowth.

Autophagy Enhanced by Microtubule- and Mitochondrion-Associated MAP1S Suppresses Genome Instability and Hepatocarcinogenesis
Rui Xie, Fen Wang, Wallace L. McKeelhan, and Leyuan Liu

**Précis:** Autophagic capabilities are vital to curtail the effects of genomic and cellular damage that can promote carcinogenesis, in support of a functional link between aging and cancer.

Hepatitis B Virus Large Surface Antigen Promotes Liver Carcinogenesis by Activating the Sre/P3K/Akt Pathway
Haiou Liu, Jiejie Xu, Lei Zhou, Xiaoqing Yun, Lin Chen, Shanshan Wang, Linlin Sun, Yumei Wen, and Jianxin Gu

**Précis:** HBV infection is associated with an increased risk of liver cancer, but molecular insights into exactly how this virus drives hepatocarcinoma are needed to rationalize suitable targeting strategies for prevention and treatment, especially in the Far East, where liver cancer is endemic.

Phosphorylation of Carbonic Anhydrase IX Controls Its Ability to Mediate Extracellular Acidification in Hypoxic Tumors
Peter Ditte, Franck Dequiedt, Eliska Svatsova, Albeta Halikova, Anna Ohradanova-Repic, Miriam Zatovicova, Lucia Csaderova, Juraj Kopacek, Claudia T. Supuran, Silvia Pastorekova, and Jaromir Pastorek

**Précis:** Phosphorylation of carbonic anhydrase affects its ability to regulate pH in hypoxic cancer cells, suggesting a simple targeted strategy to kill these cells.
**PREVENTION AND EPIDEMIOLOGY**

**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.

**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.

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**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

**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.

**Dual IGF-1R/InsR Inhibitor BMS-754807 Synergizes with Hormonal Agents in Treatment of Estrogen-Dependent Breast Cancer**
Xiaoran 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.

**miR-221 Silencing Blocks Hepatocellular Carcinoma and Promotes Survival**
Jong-Kook Park, Takayuki Kogure, Gerard J. Nuzzo, Jinnai Jiang, Lei He, Ji Hye Kim, Mitch A. Phelps, Tracey L. Papenfuss, Carlo M. Croce, Tushar Patel, and Thomas D. Schmittgen

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

**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.

**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, Cristel/18/18e Gilbert, Loïc Lemonnier, Jessica Nakl/19/19e, Catherine Gallou-Kabani, Basma Guarmit, Aur/19/19elie 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.

TARGETS OF THE TUMOR SUPPRESSOR miR-200 IN REGULATION OF THE EPITHELIAL–MESENCHYAL 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.

LETTERS TO THE EDITOR

STK33 Kinase Is Not Essential in KRAS-Dependent Cells–Letter
Stefan Frohling 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

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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.