RESEARCH

November 1, 2011 • Volume 71 • Number 21

Contents

BREAKING ADVANCES

6559 Highlights from Recent Cancer Literature

REVIEWS

6561 PAR-1 and Thrombin: The Ties That Bind the Microenvironment to Melanoma Metastasis
Maya Zigler, Takafumi Kamiya, Emily C. Brantley, Gabriel J. Villares, and Menashe Bar-Eli

6567 Prospects for TIM3-Targeted Antitumor Immunotherapy
Shin Foong Ngiow, Michele W.L. Teng, and Mark J. Smyth

PERSPECTIVES

6572 Is Co-option a Prevailing Mechanism during Cancer Progression?
Marc Billaud and Massimo Santoro

6576 Sphingosine Kinase Inhibitors and Cancer: Seeking the Golden Sword of Hercules
Susan Pyne, Robert Bittman, and Nigel J. Pyne

PRIORITY REPORT

6583 Oxygen Is a Master Regulator of the Immunogenicity of Primary Human Glioma Cells

Précis: The efficacy of hundreds of dendritic cell vaccines currently in clinical development might be improved dramatically simply by reducing the oxygen level in tumor cell cultures that are used as source of antigens to prime the vaccine.

INTEGRATED SYSTEMS AND TECHNOLOGIES

6590 Aberrant Lipid Metabolism in Hepatocellular Carcinoma Revealed by Plasma Metabolomics and Lipid Profiling
Andrew D. Patterson, Olivier Maurhofer, Diren Beyoglu, Christian Lanz, Kristopher W. Krausz, Thomas Pabst, Frank J. Gonzalez, Jean-François Dufour, and Jeffrey R. Idle

Précis: A sophisticated set of metabolomic discovery platforms were employed in this study to define plasma markers of intermediate-stage hepatocellular carcinoma, revealing a number of new molecular alterations and illustrating the potential of this technology for developing pathophysiological understanding and discovering informative diagnostics.

MICROENVIRONMENT AND IMMUNOLOGY

6601 Antiangiogenic and Antimetastatic Activity of JAK Inhibitor AZD1480
Hong Xin, Andreas Herrmann, Karen Reckamp, Wang Zhang, Sumanta Pal, Michael Hedvat, Chunyan Zhang, Wei Liang, Anna Scuto, Shaobu Weng, Deborah Morosini, Zhu A. Cao, Michael Zinda, Robert Figlin, Dennis Huszar, Richard Jove, and Hua Yu

Précis: JAK inhibitors in clinical development effectively inhibit tumor angiogenesis and metastasis mediated by STAT3 in tumor stromal cells as well as tumor cells themselves, encouraging their broader evaluation for cancer treatment than only in malignancies characterized by JAK/STAT mutations.

6611 Targeting the Immunoregulator SRA/CD204 Potentiates Specific Dendritic Cell Vaccine-Induced T-cell Response and Antitumor Immunity
Huanfa Yi, Chunqing Guo, Xiaofei Yu, Ping Gao, Jie Qian, Daming Zuo, Masoud H. Manjili, Paul B. Fisher, John R. Subjeck, and Xiang-Yang Wang

Précis: Findings offer a straightforward strategy to enhance the potency of dendritic cell vaccines, for which Provenge is the first FDA-approved example, by targeting a pattern recognition scavenger receptor that limits the ability of dendritic cells to restore T cell-mediated antitumor immunity.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6621</td>
<td>Human Breast Tumor Cells Induce Self-Tolerance Mechanisms to Avoid NKG2D-Mediated and DNAM-Mediated NK Cell Recognition</td>
<td>Emilie Mamessier, Aude Sylvain, François Bertucci, Rémy Castellano, Pascal Finetti, Gilles Houvenaeghel, Emmanuelle Charafe-Jauret, Daniel Birnbaum, Alessandro Moretta, and Daniel Olive</td>
<td>Precise: All breast cancer subtypes develop mechanisms to escape natural killer cell-mediated immune recognition, rationalizing the development of immunotherapies that can relieve escape and/or enhance natural killer cell function.</td>
</tr>
<tr>
<td>6643</td>
<td>Human Cytomegalovirus US28 Found in Glioblastoma Promotes an Invasive and Angiogenic Phenotype</td>
<td>Liliana Soroceanu, Lisa Matlaf, Vladimir Bezrookove, Loui Harkins, Roxanne Martinez, Mary Greene, Patricia Soteropoulos, and Charles S. Cobbs</td>
<td><strong>Precise:</strong> Human cytomegalovirus infections that occur commonly in deadly brain glioblastomas may be contributing strongly to the aggressive progression which characterizes this disease, through expression of a viral G protein-like coupled receptor that can be therapeutically targeted.</td>
</tr>
<tr>
<td>6654</td>
<td>SIRT1 Is Essential for Oncogenic Signaling by Estrogen/Estrogen Receptor α in Breast Cancer</td>
<td>Selvakumar Elangovan, Sabarish Ramachandran, Narayanan Venkatesan, Sudha Ananth, Jaya P. Gnana-Prakasam, Pamela M. Martin, Darren D. Browning, Patricia V. Schoenlein, Purtur D. Prasad, Vadivel Ganapathy, and Muthusamy Thangaraju</td>
<td>Precise: Small molecule inhibitors of the histone deacetylase SIRT1 presently in clinical development may find an important application in potentiating the beneficial effects of antiestrogen treatments in breast cancer.</td>
</tr>
<tr>
<td>6665</td>
<td>MOLECULAR AND CELLULAR PATHOBIOLOGY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6666</td>
<td>Progression of Human Bronchioloalveolar Carcinoma to Invasive Adenocarcinoma Is Modeled in a Transgenic Mouse Model of K-ras-Induced Lung Cancer by Loss of the TGF-β Type II Receptor</td>
<td>Alain C. Borczuk, Marieta Sole, Ping Lu, Jinli Chen, May-Lin Wilgus, Richard A. Friedman, Steven M. Albelda, and Charles A. Powell</td>
<td>Precise: The important new model of lung cancer progression reported in this study recapitulates the genomics and clinical progression of human lung adenocarcinoma, also highlighting its control by an important TGF-β receptor.</td>
</tr>
<tr>
<td>6676</td>
<td>Plasminogen Receptor S100A10 Is Essential for the Migration of Tumor-Promoting Macrophages into Tumor Sites</td>
<td>Kyle D. Phipps, Alexi P. Surette, Paul A. O’Connell, and David M. Waisman</td>
<td>Precise: This important study reveals a pivotal signaling node in cancer progression by demonstrating that the receptor for plasminogen, a key regulator of blood coagulation and metastasis, is essential for migration of tumor-promoting macrophages into tumor sites.</td>
</tr>
<tr>
<td>6684</td>
<td>Manganese Superoxide Dismutase Is a p53-Regulated Gene That Switches Cancers between Early and Advanced Stages</td>
<td>Sanjit K. Dhar, Jitanjong Tangpong, Lukasna Chaiswing, Terry D. Oberley, and Daret K. St. Clair</td>
<td>Precise: This study reports a novel genetic model of skin carcinogenesis that reveals the importance of a linkage between ROS scavenging networks and cellular stress responses involving p53.</td>
</tr>
</tbody>
</table>
A Novel MLL5 Isoform That Is Essential to Activate E6 and E7 Transcription in HPV16/18-Associated Cervical Cancers
Chow Wenny Yew, Pei Lee, Wai Keong Chan, Vania Kai Jun Lim, Sun Kuie Tay, Theresa M.C. Tan, and Lih-Wen Deng

**Précis:** This study reports the discovery of a molecule exclusively expressed in HPV-associated cervical cancers, where it may offer a novel and disease selective therapeutic target and biomarker.

RNA Helicase DDX5 Is a p53-Independent Target of ARF That Participates in Ribosome Biogenesis

**Précis:** This study offers an answer to the long-standing question of how the tumor suppressor ARF inhibits ribosome biogenesis, which does not involve p53 but is essential to prevent Ras-induced cell transformation.

**ARID1A,** a Factor That Promotes Formation of SWI/SNF-Mediated Chromatin Remodeling, Is a Tumor Suppressor in Gynecologic Cancers
Bin Guan, Tian-Li Wang, and Ie-Ming Shih

**Précis:** A member of the SWI/SNF chromatin remodeling complex is shown to be a tumor suppressor in the development of several types of gynecological cancer, suggesting that aberrant chromatin remodeling activity has a central role in their pathogenesis.

An Iron Regulatory Gene Signature Predicts Outcome in Breast Cancer

**Précis:** This study identifies a link between genes that govern iron metabolism and breast cancer prognosis, and suggests new tools that may ultimately help guide breast cancer prognosis.

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

**Précis:** A Forkhead transcription factor controlling global chromatin structure is a pivotal organizer of G1-S cell cycle transit in castration-resistant prostate cancer.
Expression and Immunotherapeutic Targeting of the SSX Family of Cancer–Testis Antigens in Prostate Cancer

Heath A. Smith, Robert J. Cronk, Joshua M. Lang, and Douglas G. McNeel

Précis: Exclusive expression of a set of antigens expressed only in testis and metastatic prostate cancer may offer attractive targets for immunotherapy.

2-Deoxyglucose Induces Noxa-Dependent Apoptosis in Alveolar Rhabdomyosarcoma

Silvia Ramírez-Peinado, Fermín Alcázar-Limones, Laura Lagares-Tena, Nadia El Mijiyad, Alfredo Caro-Maldonado, Oscar M. Tirado, and Cristina Muñoz-Pinedo

Précis: An aggressive pediatric muscle tumor was discovered to be highly sensitive to a glycolytic inhibitor similar to one used widely in the oncology clinic for PET imaging, suggesting it might be immediately repositioned as a therapeutic to treat what is often a fatal childhood cancer.

Verticillin A Overcomes Apoptosis Resistance in Human Colon Carcinoma through DNA Methylation-Dependent Upregulation of BNIP3

Feiyan Liu, Qianqian Liu, Dafeng Yang, Wendy B. Bollag, Keith Robertson, Ping Wu, and Kebin Liu

Précis: To combat drug resistance, the primary cause of deaths from cancer, one top goal of laboratory research is to identify adjuvants that can safely and effectively cooperate with existing treatments to widen their therapeutic window of action.

Inhibition of Neurotensin Receptor 1 Selectively Sensitizes Prostate Cancer to Ionizing Radiation

Nicholas C.K. Valerie, Eli V. Casarez, John O. DaSilva, Marya E. Dunlap-Brown, Sarah J. Parsons, George P. Amorino, and Jaroslaw Dziegielewski

Précis: A receptor that is absent from normal prostate cells, but switched on in prostate cancers, offers a therapeutic target for radiosensitizing this malignancy.

Cell-Cycle Regulator Cks1 Promotes Hepatocellular Carcinoma by Supporting NF-κB-Dependent Expression of Interleukin-8

Eun-Kyoung Lee, Dae-Ghon Kim, Jang-Seong Kim, and Yeup Yoon

Précis: Findings link an important cell cycle regulator to NF-κB control of a central regulator of the inflammatory tumor microenvironment, illustrating how the cell division processes of cancer cells are perhaps invariably linked to their coordination of local immune support.

A NOTCH3-Mediated Squamous Cell Differentiation Program Limits Expansion of EMT-Competent Cells That Express the ZEB Transcription Factors


Précis: Novel insights into the progression of a class of esophageal cancers rising rapidly in incidence are provided by this mechanistic study of how Notch3 receptor signaling acts to prevent expansion of aggressive clones that can emerge during tumorigenesis.

Generation of a Mouse Model of Von Hippel–Lindau Kidney Disease Leading to Renal Cancers by Expression of a Constitutively Active Mutant of HIF1α

Leiping Fu, Gang Wang, Maria M. Shevchuk, David M. Nanus, and Lorraine J. Gudas

Précis: This study describes a new transgenic mouse model for von Hippel-Lindau (VHL) kidney disease that mimics the genetic and molecular events leading to human renal cell carcinoma.

Breast Cancer Subtype-Specific Interactions with the Microenvironment Dictate Mechanisms of Invasion

Tuyen T. Dang, Amanda M. Prechtl, and Gray W. Pearson

Précis: Real-time imaging of tumor-fibroblast interactions in breast cancer suggests how interactions with the microenvironment control malignant progression, and also how basal and luminal subtypes of breast cancer do not progress in the same way.
Tumor Necrosis Factor-α (TNF-α) Promotes c-REL/ΔNp63α Interaction and TAp73 Dissociation from Key Genes That Mediate Growth Arrest and Apoptosis in Head and Neck Cancer


Précis: Inflammatory signals in the tumor microenvironment can attenuate tumor suppressor functions in cancer cells, as illustrated by this study of how TNF-β and the NF-κB oncoprotein c-REL repress the antiproliferative and proapoptotic activities of ΔNp63-bound p73 in cancer cells harboring mutant p53.

FOXO3a-Dependent Mechanism of E1A-Induced Chemosensitization

Jen-Liang Su, Xiaoyun Cheng, Hirohito Yamaguchi, Yi-Wen Chang, Chao-Feng Hou, Dung-Fang Lee, How-Wen Ko, Kuo-Tai Hua, Ying-Nai Wang, Michael Hsiao, PoShen B. Chen, Jung-Mao Hsu, Robert C. Bast, Jr, Gabriel N. Hortobagyi, and Mien-Chie Hung

Précis: By providing a leap forward in understanding how the adenovirus oncoprotein E1A sensitizes cancer cells to paclitaxel, this study provides a strong mechanistic rationale to use E1A gene therapy which has been tested clinically as an adjuvant to chemosensitize cancers to this widely used antimitotic drug.

PGC1α Promotes Tumor Growth by Inducing Gene Expression Programs Supporting Lipogenesis

Kavita Bhalla, Bor Jang Hwang, Ruby E. Dewi, Lihui Ou, William Twaddel, Hong-bin Fang, Scott B. Vafai, Francesca Vazquez, Pere Puigserver, Laszlo Boros, and Geoffrey D. Girms

Précis: Results show how a central regulator of energy metabolism controls multiple metabolic pathways to drive carcinogenesis and cancer growth.

Binding of the JmjC Demethylase JARID1B to LSD1/NuRD Suppresses Angiogenesis and Metastasis in Breast Cancer Cells by Repressing Chemokine CCL14

Qian Li, Lei Shi, Bin Gui, Wenhua Yu, Jiamu Wang, Di Zhang, Xiao Han, Zhi Yao, and Yongfeng Shang

Précis: Findings define a novel pharmacetically tractable target that is part of an important transcriptional repression complex broadly implicated in malignant progression.

OBITUARY

On the Passing of Gerald C. Mueller, MD, PhD (1920–2010)

CORRECTIONS

Correction: A Requirement of STAT3 DNA-Binding Precludes Th-1 Immunostimulatory Gene Expression by NF-κB in Tumors

Correction: Online Publication Date for Cancer Research September 1, 2011, Article

ABOUT THE COVER

Macrophages play a key role in tumor growth, invasion, and metastasis. Phipps and colleagues identified the mechanism that controls the migration of macrophages to the tumor site. They showed that the generation of plasmin at the cell surface of the macrophage is regulated by the plasminogen receptor S100A10, and that S100A10-regulated plasmin generation is necessary for both the movement of the macrophages to the tumor site and tumor growth and vascularization. The photomicrograph shows that the vascular density, monitored by CD31 immunofluorescence (green), of Lewis lung carcinoma tumors grown in S100A10-null mice can be restored by the adoptive transfer of wild-type macrophages. For details, see the article by Phipps and colleagues on page 6676 of this issue.