**BREAKING ADVANCES**

507 Highlights from Recent Cancer Literature

**CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES**

509 Fat, Calories, and Cancer
Yves A. DeClerck

511 Observations on Radiation-Induced Lymphoid Tumors of Mice
Rakesh Kumar

**REVIEW**

513 A Breakthrough: Macrophage-Directed Cancer Immunotherapy
Charles D. Mills, Laurel L. Lenz, and Robert A. Harris

**PRIORITY REPORT**

517 VEGF-A/VEGFR Inhibition Restores Hematopoietic Homeostasis in the Bone Marrow and Attenuates Tumor Growth
Rebekah K. O’Donnell, Beverly Falcon, Jeff Hanson, Whitney E. Goldstein, Carole Perruzzi, Shahin Rafii, William C. Aird, and Laura E. Benjamin

Précis: This study provides preclinical proof of concept that the bone marrow hematopoietic niche can be directly targeted and opposed by antiangiogenic therapy.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

535 Modeling Spontaneous Metastasis following Surgery: An In Vivo-In Silico Approach
Sebastien Benzekry, Amanda Tracz, Michalis Mastri, Ryan Corbelli, Dominique Barbolosi, and John M.L. Ebos

Précis: A data-based mathematical model that assesses the impact of surgery on metastatic potential may have clinical uses to individualize adjuvant therapies that can extend cancer remission.

**MICROENVIRONMENT AND IMMUNOLOGY**

548 Citrullinated Vimentin Presented on MHC-II in Tumor Cells Is a Target for CD4+ T-Cell–Mediated Antitumor Immunity
Victoria A. Brentville, Rachael L. Metheringham, Barbara Gunn, Peter Symonds, Ian Daniels, Mohamed Gijon, Katherine Cook, Wei Xue, and Lindy G. Durrant

Précis: Results show how CD4 cells can mediate potent antitumor responses against modified self-epitopes presented on tumor cells, and they illustrate for the first time how the citrullinated peptides may offer especially attractive subjects for cancer vaccine development.

**MOLECULAR AND CELLULAR PATHOBIOLOGY**

561 Balancing Protein Stability and Activity in Cancer: A New Approach for Identifying Driver Mutations Affecting CBL Ubiquitin Ligase Activation
Minghui Li, Stephen C. Kales, Ke Ma, Benjamin A. Shoemaker, Juan Crespo-Barreto, Andrew L. Cangelosi, Stanley Lipkowitz, and Anna R. Panchenko

Précis: This study describes a new computational approach to identify the functional consequences of cancer mutations using the ubiquitin ligase CBL as a model for proof of concept.

572 HEATR1 Negatively Regulates Akt to Help Sensitize Pancreatic Cancer Cells to Chemotherapy
Tongzheng Liu, Yuan Fang, Haoxing Zhang, Min Deng, Bowen Gao, Nifang Niu, Jia Yu, SeungBaek Lee, Junglim Kim, Bo Qin, FangXie, Debra Evans, Liewei Wang, Wenhui Lou, and Zhenkun Lou

Précis: This study offers several lines of evidence for a new predictive and prognostic biomarker of chemotherapy response and outcome in pancreatic cancer patients, with additional implications for methods to sensitize pancreatic tumors to therapeutic eradication.

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### Table of Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>582</td>
<td>Aberrant Activation of Notch Signaling Inhibits PROX1 Activity to Enhance the Malignant Behavior of Thyroid Cancer Cells</td>
</tr>
<tr>
<td>594</td>
<td>DNA Hypomethylation and Histone Variant macroH2A1 Synergistically Attenuate Chemotherapy-Induced Senescence to Promote Hepatocellular Carcinoma Progression</td>
</tr>
<tr>
<td>607</td>
<td>SIGMAR1 Regulates Membrane Electrical Activity in Response to Extracellular Matrix Stimulation to Drive Cancer Cell Invasiveness</td>
</tr>
<tr>
<td>619</td>
<td>PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease</td>
</tr>
<tr>
<td>630</td>
<td>Systemic Chromosome Instability Resulted in Colonic Transcriptomic Changes in Metabolic, Proliferation, and Stem Cell Regulators in Sgo1&lt;sup&gt;−/−&lt;/sup&gt; Mice</td>
</tr>
<tr>
<td>643</td>
<td>Bereavement Is Associated with an Increased Risk of HPV Infection and Cervical Cancer: An Epidemiological Study in Sweden</td>
</tr>
<tr>
<td>652</td>
<td>Hydroxamic Acid and Benzoic Acid–Based STAT3 Inhibitors Suppress Human Glioma and Breast Cancer Phenotypes In Vitro and In Vivo</td>
</tr>
</tbody>
</table>

### PREVENTION AND EPIDEMIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>619</td>
<td>PBX3 and MEIS1 Cooperate in Hematopoietic Cells to Drive Acute Myeloid Leukemias Characterized by a Core Transcriptome of the MLL-Rearranged Disease</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

### THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>652</td>
<td>Hydroxamic Acid and Benzoic Acid–Based STAT3 Inhibitors Suppress Human Glioma and Breast Cancer Phenotypes In Vitro and In Vivo</td>
</tr>
</tbody>
</table>

*Précis:* A gene expression signature stimulated by two homeobox transcription factors in hematopoietic precursor offers intriguing new insights into how acute myeloid leukemias may arise.

*Précis:* A mouse model of chromosome instability reveals aberrant regulation of unexpected pathways and offers new targets for therapeutic and preventive strategies.

*Précis:* Women who experience the loss of an immediate family member are at a higher risk of developing cervical cancer, possibly related to an increased incidence of oncogenic HPV infections, with implications for identifying at-risk individuals who could benefit from increased screening.

*Précis:* STAT3 offers an attractive target for cancer therapy, but small molecule inhibitors with appealing pharmacologic and biologic properties in animals have been elusive.
Elucidation and Pharmacological Targeting of Novel Molecular Drivers of Follicular Lymphoma Progression

Brygida Biskińska, Mukesh Bansal, Yao Shen, Julie Tenya-Feldstein, Raju Chaganti, and Andrea Califano

Précis: Computational interrogation of human B-cell regulatory networks enables the identification of key drivers of follicular lymphoma and provides a generalized approach for the systematic analysis of drug combinations that may offer the strongest antitumor responses.

Modulation of EZH2 Expression by MEK-ERK or PI3K-AKT Signaling in Lung Cancer Is Dictated by Different KRAS Oncogene Mutations


Précis: For those lung cancer patients whose tumors harbor KRAS mutations, the specific type of mutation determines which kinase effector signaling pathways to target along with the histone methyltransferase EZH2, defined here as a novel KRAS effector.

Deguelin Analogue SH-1242 Inhibits Hsp90 Activity and Exerts Potent Anticancer Efficacy with Limited Neurotoxicity


Précis: This study reports an important advance in the development of Hsp90 inhibitors as cancer therapeutics, a drug class that is appealing in principle but limited to date by significant toxic side-effects that have impeded clinical development.

Agonists of the TRAIL Death Receptor DR5 Sensitize Intestinal Stem Cells to Chemotherapy-Induced Cell Death and Trigger Gastrointestinal Toxicity

Niklas K. Finnberg, Prashanth Gokare, Arunasalam Navaraj, Krystle A. Lang Kuhs, George Cerniglia, Hideo Yagita, Kazuyoshi Takeda, Noboru Motoyama, and Wafik S. El-Deiry

Précis: These findings suggest a strategy to reduce gastrointestinal toxicities that arise from combining chemotherapy with TRAIL death receptor agonists, with clinical implications for developing these agents for cancer therapy.

TUMOR AND STEM CELL BIOLOGY

Therapeutic Targeting of Tumor-Derived R-Spondin Attenuates β-Catenin Signaling and Tumorigenesis in Multiple Cancer Types

Cecile Chartier, Janak Raval, Fumiko Axelrod, Chris Bond, Jennifer Cain, Cristina Dee-Hoskins, Shirley Ma, Marcus M. Fischer, Jatla Shah, Jie Wei, May JI, Andrew Lam, Michelle Stroud, Wan-Ching Yen, Peter Yeung, Belinda Cancilla, Gilbert O’Young, Min Wang, Ann M. Kapoun, John Lewicki, Timothy Hoey, and Austin Gurney

Précis: R-spondin proteins are defined as enhancers of tumorigenic Wnt/β-catenin signaling, suggesting a novel mechanistic strategy to target β-catenin-driven cancers.

Recurrent MLK4 Loss-of-Function Mutations Suppress JNK Signaling to Promote Colon Tumorigenesis


Précis: This study establishes a tumor suppressor role for a kinase that is frequently inactivated by mutation in colon cancer, leading to inactivation of JNK pathway signaling, aberrant cell proliferation, and enhanced tumor growth.

Myc Induces miRNA-Mediated Apoptosis in Response to HDAC Inhibition in Hematologic Malignancies

Clare M. Adams, Scott W. Hiebert, and Christine M. Eischen

Précis: This study highlights a surprising role for Myc in activating a miRNA-mediated apoptotic program, the implications of which increase understanding of how HDAC inhibitors selectively target malignant cells.
Integrated Genomic Analysis of Pancreatic Ductal Adenocarcinomas Reveals Genomic Rearrangement Events as Significant Drivers of Disease

Stephen J. Murphy, Steven N. Hart, Geoffrey C. Halling, Sarah H. Johnson, James B. Smadbeck, Travis Drucker, Joema Felipe Lima, Fariborz Rakhshan Rohakhtar, Faye R. Harris, Farhad Kosari, Subbaya Subramanian, Gloria M. Petersen, Timothy D. Wiltshire, Benjamin R. Kipp, Mark J. Truty, Robert R. McWilliams, Fergus J. Couch, and George Vasmatzis

Précis: Large genomic rearrangements may perturb signaling pathways that drive pancreatic cancer initiation, affecting progression to the same extent as point mutations, underscoring the need for comprehensive genomic analysis to elucidate disease mechanisms.

Correction: Development of a New Tracking Tool for the Human Monomeric Laminin-γ2 Chain In Vitro and In Vivo

ABOUT THE COVER

The monomeric Casitas B-lineage lymphoma (c-Cbl, CBL) RING finger ubiquitin ligase (blue) can bind to phosphorylated RTK (orange peptide) via the TKID domain. Upon phosphorylation, CBL undergoes a large conformational change that positions the ubiquitin-conjugating enzyme E2 (green) active site close to RTK. Cancer mutation sites are mapped on the structure of the complex and are shown in yellow; Zn ions are shown as blue balls. Other stages of the CBL activation cycle are depicted in Figure 1 of the article. For details, see article by Li and colleagues on page 561.
Cancer Research

76 (3)


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