**BREAKING ADVANCES**

6077 Highlights from Recent Cancer Literature

**REVIEWS**

6079 1p36 Tumor Suppression—A Matter of Dosage?
Kai-Oliver Henrich, Manfred Schwab, and Frank Westermann

6089 Engineering Approaches for Investigating Tumor Angiogenesis: Exploiting the Role of the Extracellular Matrix
Abigail C. Hielscher and Sharon Gerecht

**PERSPECTIVE**

6097 Why Your New Cancer Biomarker May Never Work: Recurrent Patterns and Remarkable Diversity in Biomarker Failures
Scott E. Kern

**CLINICAL STUDIES**

6102 Skin-Test Infiltrating Lymphocytes Early Predict Clinical Outcome of Dendritic Cell–Based Vaccination in Metastatic Melanoma

Precis: This study offers a simple and robust cellular bioassay to predict survival in metastatic melanoma patients receiving immunotherapy at early times in their treatment by integrating multiple functions that mediate effective immune response.

**INTEGRATED SYSTEMS AND TECHNOLOGIES**

6111 Unexpected Dissemination Patterns in Lymphoma Progression Revealed by Serial Imaging within a Murine Lymph Node
Ken Ito, Bryan Ronain Smith, Natesh Parashurama, Joon-kee Yoon, Si Yeol Song, Cornelius Miething, Parag Mallick, Scott Lowe, and Sanjiv Sam Gambhir

Precis: Use of a novel in vivo multimodal imaging system reveals that seeding of lymphoma cells into peripheral lymph nodes occurs by a rapid release of large numbers of tumor cells from the spleen or bone marrow, in contrast to the accepted paradigm of metastatic seeding.

**MICROENVIRONMENT AND IMMUNOLOGY**

6119 Distinctive Features of the Differentiated Phenotype and Infiltration of Tumor-Reactive Lymphocytes in Clear Cell Renal Cell Carcinoma
Qiong J. Wang, Ken-ichi Hanada, Paul F. Robbins, Yong F. Li, and James C. Yang

Precis: Renal cancer is thought to be a highly immunogenic cancer, but it has been difficult to identify and understand the nature of the tumor-infiltrating lymphocytes before this study, which has implications for understanding the role of T-cell memory in effective immune responses in cancer.

6130 ICOS-Ligand Expression on Plasmacytoid Dendritic Cells Supports Breast Cancer Progression by Promoting the Accumulation of Immunosuppressive CD4+ T Cells
Julien Faget, Nathalie Bendriss-Vermare, Michael Gobert, Isabelle Durand, Daniel Olive, Cathy Biota, Thomas Bachelot, Isabelle Treilleux, Sophie Godard-Leon, Emilie Lavergne, Sylvie Chaubaud, Jean Yves Blay, Christophe Caux, and Christine Ménétrier-Caux

Precis: Within breast tumors, interaction between the ICOS receptor on infiltrating T cells with the ICOS ligand on infiltrating plasmacytoid dendritic cells is a pivotal determinant of immune escape and is strongly rationalized as a therapeutic target to combine with other treatments.
Distinct Patterns of Dysregulated Expression of Enzymes Involved in Androgen Synthesis and Metabolism in Metastatic Prostate Cancer Tumors
Nicholas Mitsiades, Clifford C. Sung, Nikolaus Schultz, Daniel C. Danila, Bin He, Vijay Kumar Eedunuri, Martin Fleisher, Chris Sander, Charles L. Sawyers, and Howard I. Scher

Precis: Metastatic prostate carcinomas exhibit heterogeneous and distinct patterns of dysregulated expression of enzymes involved in androgen metabolism, which can contribute to the maintenance of intratumoral androgens and AR transcriptional activity despite castrate serum levels of testosterone.

Geminin Functions Downstream of p53 in K-ras–Induced Gene Amplification of Dihydrofolate Reductase
Ling Shen, Takashi Nishioka, Jinjin Guo, and Changyan Chen

Precis: Findings provide insight into the mechanistic relationship between ras mutations and gene amplification, which occur in more than 30% of all human malignancies.

An Insertion/Deletion Polymorphism within RERT-lncRNA Modulates Hepatocellular Carcinoma Risk
Zhansheng Zhu, Xueren Gao, Yan He, Hua Zhao, Qiang Yu, Deke Jiang, Pingzhao Zhang, Xiaoping Ma, Huixing Huang, Dong Dong, Jiao Wan, Zhenyong Gu, Xinghong Jiang, Long Yu, and Yuzhen Gao

Precis: An insertion/deletion polymorphism in a novel long non-coding RNA influences liver cancer risk and affects expression of a prolyl hydroxylase for the hypoxia regulatory factor HIF-1α.

Genetic Variants in miRNAs Predict Bladder Cancer Risk and Recurrence
Meilin Wang, Haiyan Chu, Pu Li, Lin Yuan, Guangbo Fu, Lan Ma, Danni Shi, Dongyan Zhong, Na Tong, Chao Qin, Changjun Yin, and Zhengdong Zhang

Precis: MicroRNA variations in human populations may represent important sources of cancer risk and recurrence, but they are only beginning to be probed as potential theranostic markers.

Contributions of Recent and Past Sexual Partnerships on Incident Human Papillomavirus Detection: Acquisition and Reactivation in Older Women
Anne F. Rositch, Anne E. Burke, Raphael P. Viscidi, Michelle L. Silver, Kathryn Chang, and Patti E. Gravitt

Precis: Most incident HPV infection appears to be attributable to past sexual behavior at older ages, supporting a natural history model of viral latency and reactivation, which must be considered in developing recommendations for cervical cancer screening, as more highly exposed women transition through menopause in coming decades.

Ultrasound-Targeted Microbubble Destruction to Deliver siRNA Cancer Therapy
Andrew R. Carson, Charles F. McTiernan, Linda Lavery, Michelle Grata, Xiaoping Leng, Jianjun Wang, Xucai Chen, and Flordeliza S. Villanueva

Precis: This study addresses the need for pharmacological strategies to effectively target therapeutic siRNA to tumors for cancer therapy.

Targeting the Transposase Domain of the DNA Repair Component Metnase to Enhance Chemotherapy
Elizabeth A. Williamson, Leah Damiani, Andrei Leitao, Chelin Hu, Helen Hathaway, Tudor Oprea, Larry Sklar, Montaser Shaheen, Julie Bauman, Wei Wang, Jac A. Nickoloff, Suk-Hee Lee, and Robert Hromas

Precis: Findings suggest that an approved antibiotic drug might be immediately repositioned to enhance the effectiveness of DNA-damaging chemotherapies used widely as first-line treatment of metastatic cancer.

Augmentation of Therapeutic Responses in Melanoma by Inhibition of IRAK-1, –4
Ratika Srivastava, Degui Geng, Yingjia Liu, Lixin Zheng, Zhouyong Li, Mary Ann Joseph, Colleen McKenna, Navneeta Bansal, Augusto Ochoa, and Eduardo Davila

Precis: Toll-like receptors are thought to operate as proinflammatory receptors in immune cells, but this study lends credence to the idea that their frequent overexpression on cancer cells also has functional import, with potential prognostic and therapeutic implications.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6217</td>
<td>Raf Kinase Inhibitor RKIP Inhibits MDA-9/Syntenin-Mediated Metastasis in Melanoma</td>
<td>Swadesh K. Das, Sujit K. Bhutia, Upneet K. Sokhi, Belal Azab, Zhao-zhong Su, Habib Boukerche, Talha Anwar, Erika L. Moen, Devisash Chatterjee, Maurizio Pellecchia, Devanand Sarkar, and Paul B. Fisher</td>
<td>Precis: This study provides mechanistic insights into an important pathway of metastasis in melanoma, one of the most aggressive cancers, possibly stimulating new therapeutic strategies to block or reverse this process in patients.</td>
</tr>
<tr>
<td>6236</td>
<td>A Novel Evolutionarily Conserved Element Is a General Transcriptional Repressor of p21 [WAF1/CIP1]</td>
<td>Weiguo Xu, Qi Zhu, Zhenghua Wu, Hao Guo, Fengjuan Wu, Dhahir S. Mashausi, Chengjie Zheng, and Dawei Li</td>
<td>Precis: The study revealed that a low level expression of the tumor suppressor p21 is maintained by an evolutionary-conserved repression element that can be turned “on” by selected chemotherapeutic drugs to slow cancer growth.</td>
</tr>
<tr>
<td>6247</td>
<td>Halofuginone Inhibits the Establishment and Progression of Melanoma Bone Metastases</td>
<td>Patricia Juarez, Khalid S. Mohammad, Juan Juan Yin, Pierrick G. J. Fournier, Ryan C. McKenna, Holly W. Davis, Xiang H. Peng, Maria Niewolna, Delphine Javelaud, John M. Chirgwin, Alain Mauviel, and Theresa A. Guise</td>
<td>Precis: A natural product that activates the integrated stress response and modulates Tgfp17 immunity is shown here to block TGF-β induced signals that drive bone and brain metastasis in melanoma, suggesting therapeutic applications of this compound for therapy of advanced forms of this disease.</td>
</tr>
<tr>
<td>6257</td>
<td>Carbon Source and Myc Expression Influence the Antiproliferative Actions of Metformin</td>
<td>Shiva Javeshghani, Mahvash Zakikhani, Shane Austin, Miguel Bazile, Marie-Jose Blouin, Ivan Topisirovic, Julie St-Pierre, and Michael N. Pollak</td>
<td>Precis: Our studies provide new insight into factors that define the subset of cancers whose growth may be inhibited by the antidiabetic drug meformin.</td>
</tr>
<tr>
<td>6268</td>
<td>Epithelial-to-Mesenchymal Transition Induced by TGF-β1 Is Mediated by Blimp-1–Dependent Repression of BMP-5</td>
<td>Mathilde Romagnoli, Karine Belguise, Ziyang Yu, Xiaobo Wang, Esther Landesman-Bollag, David C. Seldin, Dany Chaibos, Sophie Barillé-Nion, Pascal Jézéquel, Margaret L. Seldin, and Gail E. Sonenschein</td>
<td>Precis: An important B cell regulatory factor identified as a key Ras effector is found to connect Ras and TGF-β signaling pathways, which coordinate EMT in cancer cells, a hallmark of invasion and metastatic behaviors.</td>
</tr>
<tr>
<td>6279</td>
<td>A Single-Nucleotide Substitution Mutator Phenotype Revealed by Exome Sequencing of Human Colon Adenomas</td>
<td>Sergey I. Nikolaev, Sotirios K. Sotiriou, Ioannis S. Pateras, Federico Santoni, Stavros Sougioulitzis, Henrik Edgren, Henrikki Almusa, Daniel Robyr, Michel Guipponi, Janna Saarela, Vassilis G. Gorgoulis, Stylianos E. Antonarakis, and Thanos D. Halazonetis</td>
<td>Precis: This important study suggests that precancerous lesions have already evolved a mutator phenotype that can drive malignant progression and also reveals mechanistic insights into how point mutations accumulate.</td>
</tr>
</tbody>
</table>

**TUMOR AND STEM CELL BIOLOGY**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>6247</td>
<td>Halofuginone Inhibits the Establishment and Progression of Melanoma Bone Metastases</td>
<td>Patricia Juarez, Khalid S. Mohammad, Juan Juan Yin, Pierrick G. J. Fournier, Ryan C. McKenna, Holly W. Davis, Xiang H. Peng, Maria Niewolna, Delphine Javelaud, John M. Chirgwin, Alain Mauviel, and Theresa A. Guise</td>
<td>Precis: A natural product that activates the integrated stress response and modulates Tgfp17 immunity is shown here to block TGF-β induced signals that drive bone and brain metastasis in melanoma, suggesting therapeutic applications of this compound for therapy of advanced forms of this disease.</td>
</tr>
<tr>
<td>6257</td>
<td>Carbon Source and Myc Expression Influence the Antiproliferative Actions of Metformin</td>
<td>Shiva Javeshghani, Mahvash Zakikhani, Shane Austin, Miguel Bazile, Marie-Jose Blouin, Ivan Topisirovic, Julie St-Pierre, and Michael N. Pollak</td>
<td>Precis: Our studies provide new insight into factors that define the subset of cancers whose growth may be inhibited by the antidiabetic drug meformin.</td>
</tr>
<tr>
<td>6268</td>
<td>Epithelial-to-Mesenchymal Transition Induced by TGF-β1 Is Mediated by Blimp-1–Dependent Repression of BMP-5</td>
<td>Mathilde Romagnoli, Karine Belguise, Ziyang Yu, Xiaobo Wang, Esther Landesman-Bollag, David C. Seldin, Dany Chaibos, Sophie Barillé-Nion, Pascal Jézéquel, Margaret L. Seldin, and Gail E. Sonenschein</td>
<td>Precis: An important B cell regulatory factor identified as a key Ras effector is found to connect Ras and TGF-β signaling pathways, which coordinate EMT in cancer cells, a hallmark of invasion and metastatic behaviors.</td>
</tr>
</tbody>
</table>

**Acknowledgment to Reviewers**

A Journal of the American Association for Cancer Research www.aacrjournals.org
ABOUT THE COVER

A mutator phenotype revealed in colon adenomas. Point mutations identified by exome sequencing are indicated as green dots in vertical columns. Loss of heterozygosity targeting chromosome 5 in one of these adenomas is shown by the blue circles forming horizontal lines. This matrix of data formed the basis for determining mutation rates in normal colon tissue and in precancerous adenoma lesions, revealing the presence of a mutator phenotype in the latter. For details, please see the article by Nikolaev and colleagues on page 6279.