BREAKING ADVANCES
6077 Highlights from Recent Cancer Literature

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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

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

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

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 Trelleux, Sophie Goddard-Leon, Emilie Lavergne, Sylvie Chalaud, Jean Yves Blay, Christophe Caux, and Christine Ménétrier-Caux
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
Précis: 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
Précis: 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, Pinghao Zhang, Xiaopin Ma, Huixing Huang, Dong Dong, Jiao Wan, Zhenyong Gu, Xinghong Jiang, Long Yu, and Yuzhen Gao
Précis: 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, Colleen McKenna, Naiveeta Bansal, Augusto Ochoa, and Eduardo Davila
Précis: 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 J. Silver, Kathryn Chang, and Patti E. Gravitt
Précis: 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
Précis: 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
Précis: 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 Zhong, Zhaoyang Li, Mary Ann Joseph, Colleen McKenna, Navneeta Bansal, Augusto Ochoa, and Eduardo Davila
Précis: 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.

Précis: 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.


Précis: This study provides proof-of-concept for use of a modified lentiviral-mediated gene therapy to destroy lung tumors, where expression of the therapeutic gene is controlled by a powerful antioxidant response element that is strongly upregulated in the cancer cells.

A Novel Evolutionarily Conserved Element Is a General Transcriptional Repressor of p21WAF1/CIP1 Weiguo Xu, Qi Zhu, Zhenghua Wu, Hao Guo, Fengjuan Wu, Dhahiri S. Mashausi, Chengjie Zheng, and Dawei Li

Précis: The study revealed that a low level expression of the tumor suppressor p21 is maintained by an evolutionarily-conserved repression element that can be turned “on” by selected chemotherapeutic drugs to slow cancer growth.

Halofuginone Inhibits the Establishment and Progression of Melanoma Bone Metastases 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

Précis: A natural product that activates the integrated stress response and modulates Tβ17 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.

Carbon Source and Myc Expression Influence the Antiproliferative Actions of Metformin Shiva Javeshghani, Mahvash Zakikhani, Shane Austin, Miguel Bazile, Marie-José Blouin, Ivan Topisirovic, Julie St-Pierre, and Michael N. Pollak

Précis: Our studies provide new insight into factors that define the subset of cancers whose growth may be inhibited by the antidiabetic drug metformin.

Epithelial-to-Mesenchymal Transition Induced by TGF-β1 Is Mediated by Blimp-1–Dependent Repression of BMP-5 Mathilde Romagnoli, Karine Belguise, Ziyang Yu, Xiaobo Wang, Esther Landesman-Bollag, David C. Seldin, Dany Chalbos, Sophie Barillé-Nion, Pascal Jézéquel, Margaret L. Seldin, and Gail E. Sonenshein

Précis: 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.


Précis: 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.

Acknowledgment to Reviewers
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.
Cancer Research

72 (23)


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