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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.

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.

Precis: 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. Sawyer, 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-IncRNA 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

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
Melin Wang, Haiyan Chu, Pu Li, Lin Yuan, Guangbo Fu, Lan Ma, Danni Shi, Dongyan Zhong, Na Tong, Chao Qin, Changjun Yin, and Zhendong 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, Zhaoqiang Li, Mary Ann Joseph, Colleen McKenna, Narveeta 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.
Raf Kinase Inhibitor RKIP Inhibits MDA-9/Syntenin-Mediated Metastasis in Melanoma
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.

Oxidative Stress-Regulated Lentiviral TK/GCV Gene Therapy for Lung Cancer Treatment
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, Fengjian 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 Mauriel, and Theresa A. Guise
Précis: A natural product that activates the integrated stress response and modulates Th17 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.

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.

A Single-Nucleotide Substitution Mutator Phenotype Revealed by Exome Sequencing of Human Colon Adenomas
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.
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