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831 The Dark Side of Mast Cell–Targeted Therapy in Prostate Cancer
Paola Pittoni and Mario Paolo Colombo

836 Regulation of Cancer Progression by β-Endorphin Neuron
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841 Twenty-Third Annual Pezcoller Symposium: Engineering Influences in Cancer Research
Peter Friedl, Jeff Hubbell, David Livingston, and Enrico Miëlich

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845 N-Myc Regulates Expression of the Detoxifying Enzyme Glutathione Transferase GSTP1, a Marker of Poor Outcome in Neuroblastoma

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854 Hyperpolarized 13C Spectroscopy Detects Early Changes in Tumor Vasculature and Metabolism after VEGF Neutralization
Sarah E. Bohndiek, Mikko I. Kettunen, De-en Hu, and Kevin M. Brindle

MICROENVIRONMENT AND IMMUNOLOGY

865 Metastatic Cells Can Escape the Proapoptotic Effects of TNF-α through Increased Autocrine IL-6/STAT3 Signaling
Shun Li, Ni Wang, and Pnina Brodt

Précis: This study defines an IGF-I–driven mechanism of cancer cell survival that is critical for metastatic colonization of the liver, suggesting that IGF-I receptor antagonists currently in clinical trials may have particular utility in treating colon cancers and other cancers that metastasize frequently to liver.

876 Monocytic CCR2+ Myeloid-Derived Suppressor Cells Promote Immune Escape by Limiting Activated CD8+ T-cell Infiltration into the Tumor Microenvironment

Précis: The cytokine GM-CSF, which is used to enhance white cell counts in many cancer patients, also expands a population of immune-suppressive monocytic cells that can block the entry of activated antitumor T cells into the tumor microenvironment, perhaps unwittingly contributing to immune escape.

887 CD8+ T Cells Specific for Tumor Antigens Can Be Rendered Dysfunctional by the Tumor Microenvironment through Upregulation of the Inhibitory Receptors BTLA and PD-1
Julien Fourcade, Zhaojun Sun, Ornella Pagliano, Philippe Guillaume, Immanuel F. Logescher, Cindy Sander, John M. Kirkwood, Daniel Olive, Vijay Kuchroo, and Hassane M. Zareh

Précis: This study extends knowledge concerning how an important inhibitory class of co-receptor molecules on T cells acts to block their specific cytotoxic activity against tumor cells, thereby deepening insights into how to reverse this key mechanism of immune escape in tumors for therapeutic benefit.

897 Hedgehog Signaling Inhibition Blocks Growth of Resistant Tumors through Effects on Tumor Microenvironment

Précis: This study describes an MRI imaging method that can be used to noninvasively monitor vascular disruption and normalization following VEGF blockade, addressing a clinical need to rapidly evaluate the likely impact of antiangiogenic therapy in patients.
**MOLECULAR AND CELLULAR PATHOBIOLOGY**

939 Regulation of Monocarboxylate Transporter MCT1 Expression by p53 Mediates Inward and Outward Lactate Fluxes in Tumors

Romain Boidot, Frédérique Végran, Aline Meullle, Aude Le Breton, Chantal Dessy, Pierre Sonveaux, Sarah Lizard-Nacol, and Olivier Feron

948 miR-20a Encoded by the miR-17–92 Cluster Increases the Metastatic Potential of Osteosarcoma Cells by Regulating Fas Expression

Gangxiong Huang, Kazumasa Nishimoto, Zhichao Zhou, Dennis Hughes, and Eugenie S. Kleinerman

**PREVENTION AND EPIDEMIOLOGY**

958 A Positive Feedback Signaling Loop between ATM and the Vitamin D Receptor Is Critical for Cancer Chemoprevention by Vitamin D

Huei-Ju Ting, Sayeda Yasmin-Karim, Shian-Jang Yan, Jong-Wei Hsu, Tzu-Hua Lin, Weisi Zeng, James Messing, Tsong-Jeng Sheu, Bo-Ying Bao, Willis X. Li, Edward Messing, and Yi-Fen Lee

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

969 Resistance to Selective BRAF Inhibition Can Be Mediated by Modest Upstream Pathway Activation

Fei Su, William D. Bradley, Qiongqiong Wang, Hong Yang, Lizhong Xu, Brian Higgins, Kenneth Kolinsky, Kathyrn Packman, Min Jung Kim, Kerstin Trunzer, Richard J. Lee, Kathleen Schock, Stade Carter, Thomas Albert, Soren Germer, Jim Rosinski, Mitchell Martin, Mary Ellen Simcox, Brian Lestini, David Heimbrook, and Gideon Bollag

979 Potentiation of the Novel Topoisomerase 1 Inhibitor Indenoisoquinoline LMP-400 by the Cell Checkpoint and Chk1-Chk2 Inhibitor AZD7762

Sheena M. Aris and Yves Pommier

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### Histone Deacetylase Inhibition

**Increases Levels of Choline Kinase a and Phosphocholine Facilitating Noninvasive Imaging in Human Cancers**

Mounia Beloueche-Babari, Vaitha Arunan, Helen Troy, Robert H. te Poele, Anne-Christine Wong Te Fong, L. Elizabeth Jackson, Geoffrey S. Payne, John R. Griffths, Ian R. Judson, Paul Workman, Martin O. Leach, and Yuen-Li Chung

**Précis:** Noninvasive biomarkers offer critical tools for clinical trials of targeted drugs, as illustrated in this study providing mechanistic support for the use of phosphocholine as a candidate noninvasive biomarker for imaging the pharmacodynamic response to HDAC inhibitors.

### TUMOR AND STEM CELL BIOLOGY

#### Dysregulation of Ezrin Phosphorylation Prevents Metastasis and Alters Cellular Metabolism in Osteosarcoma

Ling Ren, Sung-Hyok Hong, Qing-Rong Chen, Joseph Briggs, Jessica Cassavanga, Satish Srinivasan, Michael M. Lizardo, Arnulfo Mendoza, Ashley Y. Xia, Narayan Avadhan, Javed Khan, and Chand Khanna

**Précis:** This study offers mechanistic insights into the role of a pivotal regulator of metastasis that links the plasma cell membrane to the actin cytoskeleton, and that may act in part by linking metabolic and respiratory capacity to metastatic capability.

#### Hedgehog and Notch Signaling Regulate Self-Renewal of Undifferentiated Pleomorphic Sarcomas

Chang Ye Yale Wang, Qingxia Wei, Ilkyu Han, Shingo Sato, Ronak Ghanbari-Azar, Heather Whetstone, Raymond Poon, Jiayi Hu, Feifei Zheng, Phil Zhang, Weishi Wang, Jay S. Wunder, and Benjamin A. Alman

**Précis:** Findings suggest not only novel treatment strategies for a soft tumor subtype seen almost exclusively in the elderly, but also possible insights into its enigmatic origins of development, which have been historically controversial.

### LETTERS TO THE EDITOR

#### Impact of Epithelial Organization on Myc Expression and Activity—Letter

Johanna I. Partanen and Juha Klefstrom

#### Impact of Epithelial Organization on Myc Expression and Activity—Response

David Simpson Senthil Muthuswamy, and William P. Tansey

### CORRECTIONS

**Correction:** Endoglin Regulates Cancer–Stromal Cell Interactions in Prostate Tumors

**Correction:** Sirtuin 1 Is Upregulated in a Subset of Hepatocellular Carcinomas where It Is Essential for Telomere Maintenance and Tumor Cell Growth

**Correction:** Long Noncoding RNA HOTAIR Regulates Polycomb-Dependent Chromatin Modification and Is Associated with Poor Prognosis in Colorectal Cancers

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**ABOUT THE COVER**

Vemurafenib recently achieved FDA approval for treating patients with metastatic melanoma harboring the BRAF V600E mutation. The BRAF^{V600E}-driven uncontrolled proliferation is effectively blocked by vemurafenib, reflected in the remarkable regressions observed in the clinic. However, most patients eventually relapse, and in many instances, progression is associated with reactivation of ERK signaling, as observed by high levels of ERK phosphorylation in tumor biopsies taken at progression. The cover shows an example of a tumor biopsy taken at progression. Su and colleagues identify a novel KRAS mutation that mediates the acquired resistance of melanoma cells to vemurafenib. Both MAPK and PI3K pathways are active despite the presence of drug. Combinations of vemurafenib with either MEK or AKT inhibitors are able to overcome this resistance, providing hope that these combinations could mitigate disease relapse in patients. For details, see the article by Su and colleagues on page 969 of this issue.