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   **Précis:** These findings provide a preclinical rationale for a generalized combination strategy for cancer immunotherapy that warrants immediate clinical exploration.

### INTEGRATED SYSTEMS AND TECHNOLOGIES

3659  Novel Strategies to Enforce an Epithelial Phenotype in Mesenchymal Cells
   Ana-Maria Dragoi, Rachel Swiss, Beile Gao, and Hervé Agaïsse
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3673  Mechanisms of Resistance to Intermittent Androgen Deprivation in Patients with Prostate Cancer Identified by a Novel Computational Method
   Jason D. Morken, Aaron Packer, Rebecca A. Everett, John D. Nagy, and Yang Kuang
   **Précis:** The novel computational method described in this study may help clinicians to reestablish treatment sensitivity in their patients with advanced prostate cancer by targeting the relevant mechanism in a personalized manner.

### MICROENVIRONMENT AND IMMUNOLOGY

3684  Ly-49 Family Receptors Are Required for Cancer Immunosurveillance Mediated by Natural Killer Cells
   Megan M. Tu, Ahmad Bakur Mahmoud, Andrew Wight, Amelia Mottashed, Simon Bélangér, Mir Munir A. Rahim, Elias Abou-Samra, and Andrew P. Makrigiannis
   **Précis:** These results offer a genetic proof establishing the integral role of Ly-49 receptors in tumoral immune surveillance by natural killer cells.

### MOLECULAR AND CELLULAR PATHOBIOLOGY

3695  Slug Promotes Survival during Metastasis through Suppression of Puma-Mediated Apoptosis
   Seacho Kim, Jiahong Yao, Kimita Suyama, Xia Qian, Bin-Zhi Qian, Sanmay Bandypadhyay, Olivier Loudig, Carlos De Leon-Rodriguez, Zhen Ni Zhou, Jeffrey Segall, Fernando Macian, Larry Norton, and Rachel B. Hazan
   **Précis:** An important pathway of cell survival in cancer cells antagonizes a proapoptotic molecule first identified as a p53 target, with potential implications for a general targeting principle against metastatic disease.

3707  A Rare Polymorphic Variant of NBS1 Reduces DNA Repair Activity and Elevates Chromosomal Instability
   Yuki Yamamoto, Mamiko Miyamoto, Daisuke Tatsuda, Michiaki Kubo, Hitoshi Nakagama, Yusuke Nakamura, Hitoshi Satoh, Koichi Matsuda, Toshiki Watanabe, and Tsutomu Ohta
   **Précis:** These findings address the long-running debate concerning whether the chromosomal instability of cancer cells is cause or consequence of malignant development, offering findings that support a role in causation.

3716  Netrin-1 Promotes Medulloblastoma Cell Invasiveness and Angiogenesis, and Demonstrates Elevated Expression in Tumor Tissue and Urine of Patients with Pediatric Medulloblastoma
   Tomoshige Akino, Xueze Han, Hirohao Nakayama, Brendan McNeish, David Zurakowski, Akiko Mammoto, Michael Klagsbrun, and Edward Smith
   **Précis:** Urinary levels of an axon guidance molecule implicated in tumor cell invasion may offer a useful noninvasive biomarker to predict disease status, treatment efficacy, or the presence of an invasive phenotype in a common childhood brain tumor.
3727  VEGF Regulates Region-Specific Localization of Perivascular Bone Marrow–Derived Cells in Glioblastoma  
Kelly Burrell, Sanjay Singh, Shahrzad Jalali, Richard P. Hill, and Gelareh Zadeh 

**Précis:** Targeting perivascular bone marrow–derived cells concurrently with radiation therapy and antiangiogenic therapy provides a critical new therapeutic strategy for glioblastoma, an extremely invasive but nonmetastatic brain tumor.

3740  Autophagy Inhibition by Sustained Overproduction of IL6 Contributes to Arsenic Carcinogenesis  
Yuanlin Qi, Mingfang Zhang, Hui Li, Jacqueline A. Frank, Lu Dhi, Huijuan Liu, Zhuo Zhang, Chi Wang, and Gang Chen 

**Précis:** Procancerous inflammatory states may antagonize autophagic states that help preserve cancer cell survival in hostile microenvironments, suggesting the need to uncouple inflammation and autophagy controls to enable tumor progression.

3753  High Expression of CAI2, a 9p21-Embedded Long Noncoding RNA, Contributes to Advanced-Stage Neuroblastoma  
Lisa M. Barnhill, Richard T. Williams, Olga Cohen, Youngjin Kim, Ayse Batova, Jenna A. Mielke, Karen Messer, Minya Pu, Alice L. Yu, and Mitchell B. Diccianni 

**Précis:** These findings may explain the paradoxical overexpression of tumor suppressor p16 in pediatric neuroblastomas by defining a novel long noncoding RNA that regulates p16 and may offer a biomarker for the highest-risk disease.

3764  A Regulatory Loop Involving miR-22, Sp1, and c-Myc Modulates CD147 Expression in Breast Cancer Invasion and Metastasis  
Ling-Min Kong, Cheng-Gong Liao, Yang Zhang, Jing Xu, Yu Li, Wan Huang, Yi Zhang, Huijie Bion, and Zhi-Nan Chen 

**Précis:** This study provides insights into the regulation of a likely driver of invasion and metastasis in breast cancer, with potential implications for prognosis and therapy of advanced forms of this common disease.

3779  hMOB3 Modulates MST1 Apoptotic Signaling and Supports Tumor Growth in Glioblastoma Multiforme  
Fengyuan Tang, Lei Zhang, Gongda Xue, Debby Hynx, Yuhua Wang, Peter D. Cron, Christian Hundsrucker, Alexander Hergovich, Stephan Frank, Brian A. Hennings, and Debora Schnitz-Rohmer 

**Précis:** These results identify a novel adapter-kinase complex as a candidate therapeutic target to improve the treatment of an aggressive form of brain cancer, which is characterized by inherent drug resistance.

3790  Flotillin-1 Regulates Oncogenic Signaling in Neuroblastoma Cells by Regulating ALK Membrane Association  
Arata Tomiyama, Takamasa Uekita, Reiko Kamata, Kazuki Sasaki, Junko Takita, Miki Ohira, Akira Nakagawara, Chifumi Kitanaka, Kentaro Mori, Hideki Yamaguchi, and Ryuichi Sakai 

**Précis:** These results define a regulator protein for a receptor tyrosine kinase implicated in neuroblastoma, with implications for understanding emergence of malignant features in this disease.

**PREVENTION AND EPIDEMIOLOGY**

3802  Telomere Shortening Is Associated with Genetic Anticipation in Chinese Von Hippel–Lindau Disease Families  
Xiang-hui Ning, Ning Zhang, Teng Li, Peng-jie Wu, Xi Wang, Xue-ying Li, Shuang-he Peng, Jiang-yi Wang, Jin-chao Chen, and Kan Gong 

**Précis:** A shortening in telomere length both precedes and anticipates mutation of the tumor suppressor gene VHL in cancer cells, which appears to affect telomere maintenance.

**THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY**

3810  USP9X Downregulation Renders Breast Cancer Cells Resistant to Tamoxifen  
Hendrika M. Oosterkamp, E. Marielle Hijmans, Thijn R. Brummelkamp, Sander Canisius, Lodewyk F.A. Wessels, Wilbert Zwart, and René Bernards 

**Précis:** These findings illuminate a mechanism of resistance to a drug widely used to manage ER-positive breast cancers, and they identify a gene signature that predicts responsiveness to this drug in patients with breast cancer.

3821  Neuromedin U: A Candidate Biomarker and Therapeutic Target to Predict and Overcome Resistance to HER-Tyrosine Kinase Inhibitors  
Sweta Rani, Claire Corcoran, Liam Shiels, Serena Germano, Susan Breslin, Stephen Madden, Martina S. McDermott, Brigid C. Browne, Norma O’Donovan, John Crown, Martina Gogarty, Annette T. Byrne, and Lorraine O’Driscoll 

**Précis:** An extracellular protein that stabilizes the breast cancer oncoprotein HER2 may serve as a candidate biomarker for the action of HER2-targeting drugs, as well as a possible therapeutic target to improve their efficacy.
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<td>A Recombinant Reporter System for Monitoring Reactivation of an Endogenously DNA Hypermethylated Gene</td>
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<td>Lakshmi Gopinathan, Shawn Lu Wen Tan, V.C. Padmakumar, Vincenzo Coppola, Lino Tesserollo, and Philipp Kaldis</td>
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<td>These preclinical findings show how supraphysiologic but safe levels of selenium can be administered to selectively target human and murine leukemia stem-like cells, with immediate implications for clinical evaluation.</td>
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<td>Jesus Gonzalez Bosquet, Douglas C. Marchion, HyoSeok Chon, Johnathan M. Lancaster, and Stephen Chanock</td>
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<td>Inactivation of p53 Is Insufficient to Allow B Cells and B-Cell Lymphomas to Survive Without Dicer</td>
<td>Clare M. Adams and Christine M. Eischen</td>
<td>This study calls into question the conclusions of many preclinical studies using platinum drugs dissolved in DMSO, which was discovered to greatly attenuate the cytotoxic properties of these drugs.</td>
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NDY1/KDM2B Functions as a Master Regulator of Polycomb Complexes and Controls Self-Renewal of Breast Cancer Stem Cells

Mitochondrial Retrograde Signaling Mediated by UCP2 Inhibits Cancer Cell Proliferation and Tumorigenesis
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Correction: Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

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ABOUT THE COVER

Cancer cells overexpressing uncoupling protein 2 (UCP2), a mitochondrial carrier, shift their metabolism from glycolysis toward oxidative phosphorylation and become less proliferative and poorly tumorigenic. Indeed, immunodeficient mice implanted subcutaneously with melanoma B16F10 cells (top) developed bigger tumors than UCP2 overexpressing B16F10 cells (bottom). Our results further demonstrate that, by controlling mitochondrial substrate routing, UCP2 drives a feed-forward loop from mitochondria to AMPK and HIF, with direct impact on the transformed phenotype of cancer cells. For details, see article by Esteves and colleagues on page 3971.