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3647  **MET-Mediated Resistance to EGFR Inhibitors: An Old Liaison Rooted in Colorectal Cancer Stem Cells**

Carla Boccaccio, Paolo Luraghi, and Paolo M. Comoglio

#### PRIORITY REPORT

3652  **Antimetastatic Effects of Blocking PD-1 and the Adenosine A2A Receptor**

Deepak Mittal, Arabella Young, Kimberley Stannard, Michelle Yong, Michele W.L. Teng, Bertrand Allard, John Stagg, and Mark J. Smyth

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

3659  **Novel Strategies to Enforce an Epithelial Phenotype in Mesenchymal Cells**

Ana-Maria Dragoi, Rachel Swiss, Beile Gao, and Hervé Agaisse

**Précis:** A novel functional assay for E-cadherin expression was used in a genetic screen to identify candidate therapeutic targets to block or reverse EMT as a generalized strategy for treatment of metastatic solid tumors.

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.

#### INTEGRATED SYSTEMS AND TECHNOLOGIES

3684  **Ly49 Family Receptors Are Required for Cancer Immunosurveillance Mediated by Natural Killer Cells**

Megan M. Tu, Ahmad Bakur Mahmoud, Andrew Wight, Amelia Mottashed, Simon Bélanger, Mir Munir A. Rahim, Eliaš Abou-Samra, and Andrew P. Makrigiannis

**Précis:** These results offer a genetic proof establishing the integral role of Ly49 receptors in tumoral immune surveillance by natural killer cells.

#### MICROENVIRONMENT AND IMMUNOLOGY

3695  ** Slug Promotes Survival during Metastasis through Suppression of Puma-Mediated Apoptosis**

Seaho Kim, Jiahong Yao, Kimita Suyama, Xia Qian, Bin-Zhi Qian, Sammay Bandyopadhyay, 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, Toshiaki Watanabe, and Tsumoto 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, Hirano Nakayama, Brendan McNeish, David Zurakowski, Akiko Mamamoto, Michael Klagesbrun, 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.
VEGF Regulates Region-Specific Localization of Perivascular Bone Marrow–Derived Cells in Glioblastoma
Kelly Burrell, Sanjay Singh, Shahzad 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.

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.

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.

A Regulatory Loop Involving miR-22, Sp1, and c-Myc Modulates CD147 Expression in Breast Cancer Invasion and Metastasis
Ping-Min Kong, Cheng-Gong Liao, Yang Zhang, Jing Xu, Yu Li, Wan Huang, Yi Zhang, Huijie Bian, 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.

hMOB3 Modulates MST1 Apoptotic Signaling and Supports Tumor Growth in Glioblastoma Multiforme
Fengyuan Tang, Lei Zhang, Gongda Xue, Debby Hyx, Yuhua Wang, Peter D. Cron, Christian Hundrstucker, Alexander Hergovich, Stephan Frank, Brian A. Hemmings, and Debora Schmitz-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.

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.

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.

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.

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>Ying Cui, Frederick Hausheer, Robert Beaty, Cynthia Zahnow, Jean Pierre Issa, Frederick Bunz, and Stephen B. Baylin</td>
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<td><strong>Précis:</strong> Mechanistic investigations of the drug described in this study may offer a rationale for its use to specifically sensitize p53-mutated cancer cells to chemotherapeutics that act by causing double-strand DNA damage.</td>
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<td><strong>Précis:</strong> 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, HyeSook Chon, Johnathan M. Lancaster, and Stephen Chanock</td>
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<td><strong>Précis:</strong> 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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**TUMOR AND STEM CELL BIOLOGY**

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<td>3923</td>
<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><strong>Précis:</strong> This study of the contributions of microRNA biogenesis to malignant B-cell survival suggest a novel therapeutic opportunity to treat deadly B-cell lymphomas.</td>
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NDY1/KDM2B Functions as a Master Regulator of Polycomb Complexes and Controls Self-Renewal of Breast Cancer Stem Cells


Précis: A histone demethylase that influences two epigenetic complexes implicated in cancer may offer a target for future therapeutic modalities.

CDK4/6 and IGF1 Receptor Inhibitors Synergize to Suppress the Growth of p16INK4A-Deficient Pancreatic Cancers

Andreas M. Heilmann, Rushika M. Perera, Veronika Ecker, Brandon N. Nicolay, Nabeel Bardeesy, Cyril H. Benes, and Nicholas J. Dyson

Précis: A combination of targeted therapeutics with synergistic antiproliferative activity in pancreatic cancer cells lacking p16INK4A may have general implications for treating many human cancers characterized by the loss of this tumor suppressor.

Cyclin D1 Integrates Estrogen-Mediated DNA Damage Repair Signaling

Zhiping Li, Ke Chen, Xuanmao Jiao, Chenguang Wang, Nicole E. Willmarth, Mathew C. Casimiro, Weihua Li, Xiaoming Ju, Sung Hoon Kim, Michael P. Lisanti, John A. Katzenellenbogen, and Richard G. Pestell

Précis: A dissociable cytoplasmic function of cyclin D1 that delays the DNA damage response represents yet another nonnuclear feature of this cancer gene contributing to estrogen-mediated breast tumorigenesis.

Mitochondrial Retrograde Signaling Mediated by UCP2 Inhibits Cancer Cell Proliferation and Tumorigenesis

Pauline Esteves, Claire Pecqueur, Céline Ransy, Catherine Esnous, Véronique Lenoir, Frédéric Bouilloud, Anne-Laure Bulteau, Anne Lombès, Carna Prig-Buus, Daniel Ricquier, and Marie-Clotilde Alves-Guerra

Précis: These provocative findings suggest that reorienting the function of mitochondria in cancer cells to favor energy production through oxidative phosphorylation is sufficient to restrict malignant conversion.

Genome-wide Profiling of AP-1–Regulated Transcription Provides Insights into the Invasiveness of Triple-Negative Breast Cancer

Chunyan Zhao, Yichun Qiao, Philip Jonsson, Jian Wang, Li Xu, Pegah Rouhi, Indranil Sinha, Yihai Cao, Cecilia Williams, and Karin Dahlman-Wright

Précis: This study illuminates the pathways through which an aggressive subtype of breast cancer acquires invasive and proliferative properties.

The TGFβ–miR200–MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors

Evgeny Izumchenko, Xiaofei Chang, Christina Michaillidou, Luciane Kagohara, Rajani Ravi, Keren Paz, Mariana Brait, Mohammad Hoque, Shizhang Ling, Atul Bedi, and David Sidransky

Précis: These results suggest a molecular metric that may predict the differential response to EGFR inhibitors in patients with tumors that express wild-type EGFR, with immediate implications for clinical evaluation.

Correction: Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States
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.