

Cancer Research Table of Contents



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BREAKING ADVANCES

- 3645** Highlights from Recent Cancer Literature

REVIEW

- 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 Staggs, and Mark J. Smyth
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 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.

MICROENVIRONMENT AND IMMUNOLOGY

- 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, Elias Abou-Samra, and Andrew P. Makriganis
Précis: These results offer a genetic proof establishing the integral role of Ly49 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**
Seaho Kim, Jiahong Yao, Kimita Suyama, Xia Qian, Bin-Zhi Qian, Sanmay 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, 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, Xuezhe Han, Hironao 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.

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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 Dai, Huijuan Liu, Zhuo Zhang, Chi Wang, and Gang Chen

Précis: Procarcinogenic 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, Lei Bao, 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 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.

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. 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.

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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- 3834** **A Recombinant Reporter System for Monitoring Reactivation of an Endogenously DNA Hypermethylated Gene**
 Ying Cui, Frederick Hausheer, Robert Beaty, Cynthia Zahnow, Jean Pierre Issa, Frederick Bunz, and Stephen B. Baylin
Précis: These findings offer a new tool and insights for devising optimal clinical experiments to evaluate epigenetic therapies aimed at improving the management and prevention of cancer.
- 3844** **Monoclonal Antibody Targeting of the Cell Surface Molecule TM4SF5 Inhibits the Growth of Hepatocellular Carcinoma**
Sanghoon Kwon, Kyung-Chan Choi, Young-Eun Kim, Yang-Wha Ha, Dongbum Kim, Byoung Kwon Park, Guang Wu, Doo-Sik Kim, Younghee Lee, and Hyung-Joo Kwon
Précis: This work offers a preclinical proof of concept for a cell surface molecule expressed widely in liver cancers as an appealing target for antibody therapeutics.
- 3857** **Mechanisms Promoting Escape from Mitotic Stress-Induced Tumor Cell Death**
Rebecca Sinnott, Leah Winters, Brittany Larson, Daniela Mytsa, Patrick Taus, Kathryn M. Cappell, and Angeliq W. Whitehurst
Précis: Resistance to mitotic poisons like paclitaxel may be achieved by premature exit from mitosis, such that therapeutic strategies to enhance mitotic arrest in the presence of such poisons may restore their therapeutic benefits.
- 3870** **Loss of Cdk2 and Cyclin A2 Impairs Cell Proliferation and Tumorigenesis**
Lakshmi Gopinathan, Shawn Lu Wen Tan, V.C. Padmakumar, Vincenzo Coppola, Lino Tessarollo, and Philipp Kaldis
Précis: These results suggest a rationale to explore cancer cell-targeted combinations of Cdk1 and Cdk2 inhibitors as a general approach for cancer therapy.
- 3880** **CBP-93872 Inhibits NBS1-Mediated ATR Activation, Abrogating Maintenance of the DNA Double-Strand Break-Specific G₂ Checkpoint**
Takahisa Hirokawa, Bunsyo Shiotani, Midori Shimada, Kazuhiro Murata, Yoshikazu Johmura, Mayumi Haruta, Hidetoshi Tahara, Hiromitsu Takeyama, and Makoto Nakanishi
Précis: 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.
- 3890** **Selenium Suppresses Leukemia through the Action of Endogenous Eicosanoids**
Ujjawal H. Gandhi, Naveen Kaushal, Shailaja Hegde, Emily R. Finch, Avinash K. Kudva, Mary J. Kennett, Craig T. Jordan, Robert F. Paulson, and K. Sandeep Prabhu
Précis: 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.
- 3902** **Analysis of Chemotherapeutic Response in Ovarian Cancers Using Publicly Available High-Throughput Data**
Jesus Gonzalez Bosquet, Douglas C. Marchion, HyeSook Chon, Johnathan M. Lancaster, and Stephen Chanock
Précis: By integrating diverse high-throughput biological data, this study defines a robust molecular signature that could predict the chemoresponse of patients with serous ovarian cancer, nearly a third of whom will not typically respond to chemotherapy, with implications for improving personalized care in this setting.
- 3913** **Say No to DMSO: Dimethylsulfoxide Inactivates Cisplatin, Carboplatin, and Other Platinum Complexes**
Matthew D. Hall, Katherine A. Telma, Ki-Eun Chang, Tobie D. Lee, James P. Madigan, John R. Lloyd, Ian S. Goldlust, James D. Hoeschele, and Michael M. Gottesman
Précis: 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.

TUMOR AND STEM CELL BIOLOGY

- 3923** **Inactivation of p53 Is Insufficient to Allow B Cells and B-Cell Lymphomas to Survive Without Dicer**
Clare M. Adams and Christine M. Eischen
Précis: This study of the contributions of microRNA biogenesis to malignant B-cell survival suggest a novel therapeutic opportunity to treat deadly B-cell lymphomas.

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3935 NDY1/KDM2B Functions as a Master Regulator of Polycomb Complexes and Controls Self-Renewal of Breast Cancer Stem Cells

Filippos Kottakis, Parthena Foltopoulou, Ioannis Sanidas, Patricia Keller, Ania Wronski, Benjamin T. Dake, Scott A. Ezell, Zhu Shen, Stephen P. Naber, Philip W. Hinds, Elizabeth McNiell, Charlotte Kuperwasser, and Philip N. Tschlis

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

3947 CDK4/6 and IGF1 Receptor Inhibitors Synergize to Suppress the Growth of p16^{INK4A}-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 p16^{INK4A} may have general implications for treating many human cancers characterized by the loss of this tumor suppressor.

3959 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.

3971 Mitochondrial Retrograde Signaling Mediated by UCP2 Inhibits Cancer Cell Proliferation and Tumorigenesis



Pauline Esteves, Claire Pecqueur, Céline Ransy, Catherine Esnous, Véronique Lenoir, Frédéric Bouillaud, Anne-Laure Bulteau, Anne Lombès, Carina Prip-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.

3983 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.

3995 The TGFβ-miR200-MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors

Evgeny Izumchenko, Xiaofei Chang, Christina Michailidi, 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

4006 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.

