


## BREAKING INSIGHTS

- 5479** Highlights from Recent Cancer Literature

## REVIEWS

- 5481** Low-Molecular-Weight Cyclin E in Human Cancer: Cellular Consequences and Opportunities for Targeted Therapies  
Joseph A. Caruso, Mylinh T. Duong, Jason P. W. Carey, Kelly K. Hunt, and Khandan Keyomarsi
- 5492**  Diverse Functions of Macrophages in Different Tumor Microenvironments  
Ming Yang, Daniel McKay, Jeffrey W. Pollard, and Claire E. Lewis

## CANCER RESEARCH HIGHLIGHTS

- 5504** Sexual Inequality in the Cancer Cell  
Arthur P. Arnold and Christine M. Distcheche  
*See related articles by Li et al., p. 5527, and Lopes-Ramos et al., p. 5538*

## PERSPECTIVE

- 5506** Specific Targeting of Oncogenes Using CRISPR Technology  
Felix Oppel, Matthias Schürmann, Peter Goon, Andreas E. Albers, and Holger Sudhoff

## PRIORITY REPORTS

- 5513** Loss of MST/Hippo Signaling in a Genetically Engineered Mouse Model of Fusion-Positive Rhabdomyosarcoma Accelerates Tumorigenesis  
Kristianne M. Oristian, Lisa E.S. Crose, Nina Kuprasertkul, Rex C. Bentley, Yi-Tzu Lin, Nerissa Williams, David G. Kirsch, and Corinne M. Linardic  
*Significance: A novel mouse model sheds light on the critical role of Hippo/MST downregulation in PAX3-FOXO1-positive rhabdomyosarcoma tumorigenesis.*

- 5521** Glutamate-Weighted Chemical Exchange Saturation Transfer Magnetic Resonance Imaging Detects Glutaminase Inhibition in a Mouse Model of Triple-Negative Breast Cancer  
Rong Zhou, Puneet Bagga, Kavindra Nath, Hari Hariharan, David A. Mankoff, and Ravinder Reddy  
*Significance: A sensitive method enables noninvasive detection of tumor response to inhibitors of glutamine metabolism.*

## GENOME AND EPIGENOME

- 5527** Sex Differences in Cancer Driver Genes and Biomarkers  
Constance H. Li, Syed Haider, Yu-Jia Shiah, Kevin Thai, and Paul C. Boutros  
*Significance: This study provides a comprehensive catalog of sex differences in somatic alterations, including in cancer driver genes, which influence prognostic biomarkers that predict patient outcome after definitive local therapy.*

- 5538** Gene Regulatory Network Analysis Identifies Sex-Linked Differences in Colon Cancer Drug Metabolism  
Camila M. Lopes-Ramos, Marieke L. Kuijjer, Shuji Ogino, Charles S. Fuchs, Dawn L. DeMeo, Kimberly Glass, and John Quackenbush  
*Significance: A network-based approach reveals that sex-specific patterns of gene targeting by transcriptional regulators are associated with survival outcome in colon cancer. This approach can be used to understand how sex influences progression and response to therapies in other cancers.*

## MOLECULAR CELL BIOLOGY

- 5548**  Canonical Wnt Signaling Remodels Lipid Metabolism in Zebrafish Hepatocytes following Ras Oncogenic Insult  
Yuxiao Yao, Shaoyang Sun, Jingjing Wang, Fei Fei, Zhaoru Dong, Ai-Wu Ke, Ruoyu He, Lei Wang, Lili Zhang, Min-Biao Ji, Qiang Li, Min Yu, Guo-Ming Shi, Jia Fan, Zhiyuan Gong, and Xu Wang  
*Significance: These findings identify FA desaturation as a significant downstream therapeutic target for antagonizing the combinatorial effects of Wnt and Ras signaling pathways in hepatocellular carcinoma.*

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## 5561 Replication Protein A Availability during DNA Replication Stress Is a Major Determinant of Cisplatin Resistance in Ovarian Cancer Cells

François Bélanger, Emile Fortier, Maxime Dubé, Jean-François Lemay, Rémi Buisson, Jean-Yves Masson, Abdelhamid Elsherbiny, Santiago Costantino, Euridice Carmona, Anne-Marie Mes-Masson, Hugo Wurtele, and Elliot Drobetsky

**Significance:** The influence of replication protein A exhaustion on cisplatin sensitivity harbors important implications toward improving therapy of various cancers that initially respond to platinum-based agents but later relapse due to intrinsic or acquired drug resistance.

## TUMOR BIOLOGY AND IMMUNOLOGY

### 5574 Computational Characterization of Suppressive Immune Microenvironments in Glioblastoma



Suvi Luoto, Ismail Hermelo, Elisa M. Vuorinen, Paavo Hannus, Juha Kesseli, Matti Nykter, and Kirsi J. Granberg

**Significance:** This study utilizes a computational approach to characterize the immune environments in glioblastoma and shows that glioblastoma immune microenvironments can be classified into three major subgroups, which are linked to typical glioblastoma alterations such as IDH mutation, NF1 inactivation, and CDK4-MARCH9 locus amplification.

### 5586 A RIPK3-PGE<sub>2</sub> Circuit Mediates Myeloid-Derived Suppressor Cell–Potentiated Colorectal Carcinogenesis



Guifang Yan, Huakan Zhao, Qi Zhang, Yu Zhou, Lei Wu, Juan Lei, Xiang Wang, Jiangang Zhang, Xiao Zhang, Lu Zheng, Guangsheng Du, Weidong Xiao, Bo Tang, Hongming Miao, and Yongsheng Li

**Significance:** A novel signaling circuit involving RIPK3 and PGE<sub>2</sub> enhances accumulation and immunosuppressive activity of MDSC, implicating its potential as a therapeutic target in anticancer immunotherapy.

### 5600 Macrophage-Derived Neuropilin-2 Exhibits Novel Tumor-Promoting Functions



Sohini Roy, Arup K. Bag, Samikshan Dutta, Navatha Shree Polavaram, Ridwan Islam, Samuel Schellenburg, Jasjit Banwait, Chittibabu Guda, Sophia Ran, Michael A. Hollingsworth, Rakesh K. Singh, James E. Talmadge, Michael H. Muders, Surinder K. Batra, and Kaustubh Datta

**Significance:** Neuropilin-2 in macrophages promotes tumor growth by regulating efferocytosis of apoptotic tumor cells and orchestrating immune suppression.

## 5618 Inhibition of the Stromal p38MAPK/MK2 Pathway Limits Breast Cancer Metastases and Chemotherapy-Induced Bone Loss

Bhavna Murali, Qihao Ren, Xianmin Luo, Douglas V. Faget, Chun Wang, Radia Marie Johnson, Tina Grusso, Kevin C. Flanagan, Yujie Fu, Kathleen Leahy, Elise Alspach, Xinming Su, Michael H. Ross, Barry Burnette, Katherine N. Weilbaeher, Morag Park, Gabriel Mbalaviele, Joseph B. Monahan, and Sheila A. Stewart

**Significance:** Pharmacologically targeting the stromal p38MAPK-MK2 pathway limits metastatic breast cancer growth, preserves bone quality, and extends survival.

## 5631 Actin Cytoskeleton Remodeling Drives Breast Cancer Cell Escape from Natural Killer–Mediated Cytotoxicity



Antoun Al Absi, Hannah Wurzer, Coralie Guerin, Celine Hoffmann, Flora Moreau, Xianqing Mao, Joshua Brown-Clay, Rémi Petrolli, Carla Pou Casellas, Monika Dieterle, Jean-Paul Thiery, Salem Chouaib, Guy Berchem, Bassam Janji, and Clément Thomas

**Significance:** These findings establish the pivotal role of the actin cytoskeleton in driving breast cancer cell resistance to natural killer cells, a subset of cytotoxic lymphocytes with important roles in innate antitumor immunity.

## 5644 Inhibition of Casein Kinase 2 Disrupts Differentiation of Myeloid Cells in Cancer and Enhances the Efficacy of Immunotherapy in Mice

Ayumi Hashimoto, Chan Gao, Jerome Mastio, Andrew Kossenkov, Scott I. Abrams, Ashok V. Purandare, Heshani Desilva, Susan Wee, John Hunt, Maria Jure-Kunkel, and Dmitry I. Gabrilovich

**Significance:** These findings demonstrate the modulatory effects of casein kinase 2 inhibitors on myeloid cell differentiation in the tumor microenvironment, which subsequently synergize with the antitumor effects of checkpoint inhibitor CTLA4.

## TRANSLATIONAL SCIENCE

### 5656 Discovery and Characterization of Dual Inhibitors of MDM2 and NFAT1 for Pancreatic Cancer Therapy

Wei Wang, Jiang-Jiang Qin, Sukesh Voruganti, Bhavitavya Nijampatnam, Sadanandan E. Velu, Ke-He Ruan, Ming Hu, Jianwei Zhou, and Ruiwen Zhang

**Significance:** These findings suggest that pharmacological inhibition of both MDM2 and NFAT1 is a promising strategy for the treatment of pancreatic cancer, even in tumors lacking functional p53.

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**5668** Transcriptomics and Transposon Mutagenesis Identify Multiple Mechanisms of Resistance to the FGFR Inhibitor AZD4547

Sjors M. Kas, Julian R. de Ruiter, Koen Schipper, Eva Schut, Lorenzo Bombardelli, Ellen Wientjens, Anne Paulien Drenth, Renske de Korte-Grimmerink, Sunny Mahakena, Christopher Phillips, Paul D. Smith, Sjoerd Klarenbeek, Koen van de Wetering, Anton Berns, Lodewyk F.A. Wessels, and Jos Jonkers

*Significance:* These findings demonstrate that a combined approach of transcriptomics and insertional mutagenesis in vivo is an effective method for identifying potential targets to overcome resistance to therapy in the clinic.

**5680** ErbB3 Targeting Enhances the Effects of MEK Inhibitor in Wild-Type BRAF/NRAS Melanoma

Claudia Capparelli, Timothy J. Purwin, Shea A. Heilman, Inna Chervoneva, Peter A. McCue, Adam C. Berger, Michael A. Davies, Jeffrey E. Gershenwald, Clemens Krepler, and Andrew E. Aplin

*Significance:* This work suggests a mechanism by which NRG1 regulates the sensitivity of WT NRAS/BRAF melanomas to MEK inhibitors and provides rationale for combining MEK inhibitors with anti-ErbB2/ErbB3 antibodies in these tumors.

**5694** Tailoring Chemotherapy for the African-Centric S47 Variant of TP53

Thibaut Barnoud, Anna Budina-Kolomets, Subhasree Basu, Julia I.-Ju Leu, Madeline Good, Che-Pei Kung, Jingjing Liu, Qin Liu, Jessie Villanueva, Rugang Zhang, Donna L. George, and Maureen E. Murphy

*Significance:* A rare African-derived, radioresistant p53 SNP provides proof of principle that chemotherapy can be tailored to TP53 genotype.

## CONVERGENCE AND TECHNOLOGIES

**5706** IFN $\gamma$  PET Imaging as a Predictive Tool for Monitoring Response to Tumor Immunotherapy

Heather M. Gibson, Brooke N. McKnight, Agnes Malysa, Greg Dyson, Wendy N. Wiesend, Claire E. McCarthy, Joyce Reyes, Wei-Zen Wei, and Nerissa T. Viola-Villegas

*Significance:* This study presents a novel approach to monitor therapeutic outcomes via IFN $\gamma$ -targeted positron emission tomography.

## CORRECTION

**5718** Correction: Targeting Vascular Endothelial-Cadherin in Tumor-Associated Blood Vessels Promotes T-cell-Mediated Immunotherapy

## RETRACTION

**5719** Retraction: Dicer Elicits Paclitaxel Chemosensitization and Suppresses Cancer Stemness in Breast Cancer by Repressing AXL

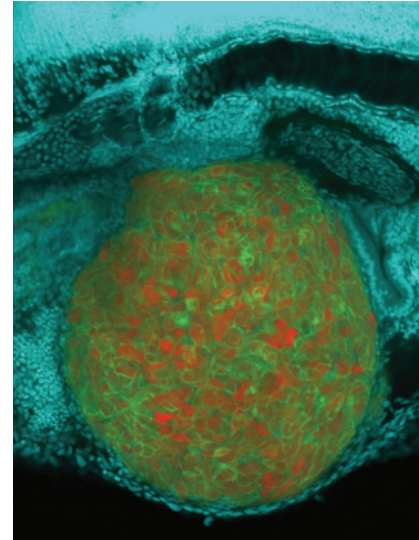
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## ABOUT THE COVER

The components and transcriptional targets of the canonical Wnt signaling pathway are frequently altered and serve as major oncogenic drivers in hepatocellular carcinoma. Zebrafish larvae emerged as unique models for studying early stage tumorigenesis due to their small size and optical transparency. In a triple transgenic zebrafish larva, *fabp10a:TetOn*; *TRE:GAL4-VP16* expresses the inducible transactivator TetOn via the hepatocyte-specific promoter; *TRE:ABC-P2A-tcf712* expresses human *CTNNB1* carrying four typical mutations and zebrafish *tcf712* ectopically in the zebrafish liver; *TCFSiam:mCherry*, a transcriptional reporter for canonical Wnt activity, labels the Wnt-responsive cells. Meanwhile, *TRE:εGFP-KrasV12* conditionally activates Ras signaling. Together, the zebrafish larva displays significant hepatomegaly and severe hyperplasia within three days in doxycycline induction, with double oncogenic pathway activated. For details, see article by Yao and colleagues on page 5548.



# Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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