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**ACR**  
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- 4653 **Therapies with Diverse Mechanisms of Action Kill Cells by a Similar Exponential Process in Advanced Cancers**  
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- 4663 **Resistance to Chemotherapy: Patient Variability and Cellular Heterogeneity**  
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- 4676 **Kinase Domain Activation of FGFR2 Yields High-Grade Lung Adenocarcinoma Sensitive to a Pan-FGFR Inhibitor in a Mouse Model of NSCLC**  
Jeremy H. Tchaicha, Esra A. Akbay, Abigail Altabef, Oliver R. Mikse, Eiki Kikuchi, Kevin Rhee, Rachel G. Liao, Roderick T. Bronson, Lynette M. Sholl, Matthew Meyerson, Peter S. Hammerman, and Kwok-Kin Wong  
*Précis:* In developing a unique mouse model of lung adenocarcinoma, this study may improve what have been limited opportunities for preclinical drug discovery and development in this setting.

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## INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4685 Polarization-Sensitive Multimodal Imaging for Detecting Breast Cancer**  
Rakesh Patel, Ashraf Khan, Robert Quinlan, and Anna N. Yaroslavsky  
*Précis:* This study describes a novel noninvasive imaging method that allows for rapid and accurate intraoperative detection of breast cancer margins.
- 4694 A Search for Novel Cancer/Testis Antigens in Lung Cancer Identifies VCX/Y Genes, Expanding the Repertoire of Potential Immunotherapeutic Targets**  
Ayumu Taguchi, Allen D. Taylor, Jaime Rodriguez, Müge Çeliktaş, Hui Liu, Xiaotu Ma, Qing Zhang, Chee-Hong Wong, Alice Chin, Luc Girard, Carmen Behrens, Wan L. Lam, Stephen Lam, John D. Minna, Ignacio I. Wistuba, Adi F. Gazdar, and Samir M. Hanash  
*Précis:* The perspective afforded by this study confirms the suspicion that prospects for effective immunotherapy are far more likely to emerge from targeting multiple tumor antigens than single tumor antigens.

## MICROENVIRONMENT AND IMMUNOLOGY

- 4706 Osteopontin Shapes Immunosuppression in the Metastatic Niche**  
Sabina Sangaletti, Claudio Tripodo, Sara Sandri, Ilaria Torselli, Caterina Vitali, Chiara Ratti, Laura Botti, Alessia Burocchi, Rossana Porcasi, Andrea Tomirotti, Mario P. Colombo, and Claudia Chiodoni  
*Précis:* Activities of a prometastatic molecule appear to differ to some extent when produced by tumor cells versus host immune cells; however, from either source it helps establish local immunosuppression within metastatic sites.
- 4720 IL-1 $\beta$ -Mediated Repression of microRNA-101 Is Crucial for Inflammation-Promoted Lung Tumorigenesis**  
Lin Wang, Ling-Fei Zhang, Jing Wu, Shu-Jun Xu, Yang-Yang Xu, Dangsheng Li, Jia-Tao Lou, and Mo-Fang Liu  
*Précis:* microRNA-101 provides a molecular connection between pathogenic inflammation and lung tumorigenesis by regulating Lin28B, an oncogenic RNA-binding protein with pleiotropic roles in cancer including stem-like cell function.

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4731 Hsp70–Bag3 Interactions Regulate Cancer-Related Signaling Networks**  
Teresa A. Colvin, Vladimir L. Gabai, Jianlin Gong, Stuart K. Calderwood, Hu Li, Suryaram Gummuluru, Olga N. Matchuk, Svetlana G. Smirnova, Nina V. Orlova, Irina A. Zamulaeva, Mikel Garcia-Marcos, Xiaokai Li, Z.T. Young, Jennifer N. Rauch, Jason E. Gestwicki, Shinichi Takayama, and Michael Y. Sherman  
*Précis:* These results offer preclinical proof-of-concept for an Hsp70 regulatory complex as an appealing anticancer target for the generalized treatment of human malignancy.
- 4741 NACK Is an Integral Component of the Notch Transcriptional Activation Complex and Is Critical for Development and Tumorigenesis**  
Kelly L. Weaver, Marie-Clotilde Alves-Guerra, Ke Jin, Zhiqiang Wang, Xiaoqing Han, Prathibha Ranganathan, Xiaoxia Zhu, Thiago DaSilva, Wei Liu, Francesca Ratti, Renee M. Demarest, Cristos Tzimas, Meghan Rice, Rodrigo Vasquez-Del Carpio, Nadia Dahmane, David J. Robbins, and Anthony J. Capobianco  
*Précis:* This study illuminates a novel critical part of the Notch receptor signaling pathway, which has emerged as an important driver of a variety of aggressive human cancers.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

- 4752 Antitumor Effects in Hepatocarcinoma of Isoform-Selective Inhibition of HDAC2**  
Yun-Han Lee, Daekwan Seo, Kyung-Ju Choi, Jesper B. Andersen, Min-Ah Won, Mitsuteru Kitade, Luis E. Gómez-Quiroz, Adam D. Judge, Jens U. Marquardt, Chiara Raggi, Elizabeth A. Conner, Ian MacLachlan, Valentina M. Factor, and Snorri S. Thorgeirsson  
*Précis:* Systemic inactivation of a disease-specific HDAC isoform can achieve therapeutic efficacy, as shown by this preclinical proof-of-concept study for treatment of liver cancer.
- 4762 Combined SFK/mTOR Inhibition Prevents Rapamycin-Induced Feedback Activation of AKT and Elicits Efficient Tumor Regression**  
Jennifer L. Yori, Kristen L. Lozada, Darcie D. Seachrist, Jonathan D. Mosley, Fadi W. Abdul-Karim, Christine N. Booth, Chris A. Flask, and Ruth A. Keri  
*Précis:* Results from this combination therapy study may help improve the mainly inefficacious effects of mTOR inhibitors in clinical trials, addressing the weaknesses of an erstwhile general approach to cancer cell eradication.



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- 4772 Immediate Utility of Two Approved Agents to Target Both the Metabolic Mevalonate Pathway and Its Restorative Feedback Loop**  
Aleksandra Pandya, Peter J. Mullen, Manpreet Kalkat, Rosemary Yu, Janice T. Pong, Zhihua Li, Suzanne Trudel, Karl S. Lang, Mark D. Minden, Aaron D. Schimmer, and Linda Z. Penn

**Précis:** This article provides an excellent illustration of polypharmacology discovery by tapping the existing armamentarium of approved drugs to identify immediately tractable new experimental therapies for clinical evaluation.

- 4783 AMPK Reverses the Mesenchymal Phenotype of Cancer Cells by Targeting the Akt–MDM2–Foxo3a Signaling Axis**  
Chih-Chien Chou, Kuen-Haur Lee, I-Lu Lai, Dasheng Wang, Xiaokui Mo, Samuel K. Kulp, Charles L. Shapiro, and Ching-Shih Chen

**Précis:** This work illuminates a mechanism of EMT limitation in cancer cells, along with preclinical support for a tractable therapeutic strategy to reverse mesenchymal phenotypes associated with invasion and metastasis.

- 4796 Neuronal Pentraxin 2 Supports Clear Cell Renal Cell Carcinoma by Activating the AMPA-Selective Glutamate Receptor-4**  
Christina A. von Roemeling, Derek C. Radisky, Laura A. Marlow, Simon J. Cooper, Stefan K. Grebe, Panagiotis Z. Anastasiadis, Han W. Tun, and John A. Copland

**Précis:** A secreted protein exclusively studied in the context of neuronal cell function appears to act through a calcium signaling pathway to support the pathogenicity of deadly kidney cancers, with immediate implications for a possible clinical treatment strategy.

- 4811 Pyrvinium Attenuates Hedgehog Signaling Downstream of Smoothed**  
Bin Li, Dennis Liang Fei, Colin A. Flaveny, Nadia Dahmane, Valérie Baubet, Zhiqiang Wang, Feng Bai, Xin-Hai Pei, Jezabel Rodriguez-Blanco, Brian Hang, Darren Orton, Lu Han, Baolin Wang, Anthony J. Capobianco, Ethan Lee, and David J. Robbins

**Précis:** An FDA-approved pinworm drug with potent activity as a casein kinase-1 $\alpha$  agonist is found to robustly inhibit Hedgehog signaling in tumors, including those resistant to existing Hedgehog pathway inhibitors, with immediate implications for clinical testing.

- 4822 Definition of PKC- $\alpha$ , CDK6, and MET as Therapeutic Targets in Triple-Negative Breast Cancer**

Yi-Hsin Hsu, Jun Yao, Li-Chuan Chan, Ting-Jung Wu, Jennifer L. Hsu, Yueh-Fu Fang, Yongkun Wei, Yun Wu, Wen-Chien Huang, Chien-Liang Liu, Yuan-Ching Chang, Ming-Yang Wang, Chia-Wei Li, Jia Shen, Mei-Kuang Chen, Aysegul A. Sahin, Anil Sood, Gordon B. Mills, Dihua Yu, Gabriel N. Hortobagyi, and Mien-Chie Hung

**Précis:** These findings define three kinases critical for growth of an aggressive subtype of breast cancer, offering a preclinical rationale to target their activity as an effective therapy.

- 4836 Mutant IDH1-Driven Cellular Transformation Increases RAD51-Mediated Homologous Recombination and Temozolomide Resistance**  
Shigeo Ohba, Joydeep Mukherjee, Wendy L. See, and Russell O. Pieper

**Précis:** Mutation of a key metabolic contributor to glioma development indirectly enhances homologous recombination-based repair of DNA damage triggered by the chemotherapy drug temozolomide, offering an explanation for the intrinsic resistance of gliomas to this drug and a rational path forward toward their eradication.

- 4845 The RAC1 P29S Hotspot Mutation in Melanoma Confers Resistance to Pharmacological Inhibition of RAF**  
Ian R. Watson, Liren Li, Peter K. Cabeceiras, Mozhdeh Mahdavi, Tony Gutschner, Giannicola Genovese, Guocan Wang, Zhuangna Fang, James M. Tepper, Katherine Stemke-Hale, Kenneth Y. Tsai, Michael A. Davies, Gordon B. Mills, and Lynda Chin

**Précis:** This timely report suggests a novel predictive biomarker for the efficacious response of melanoma patients to BRAF inhibitors, the most effective use of which has yet to be fully elucidated.

## TUMOR AND STEM CELL BIOLOGY

- 4853 Chromosomal Instability Selects Gene Copy-Number Variants Encoding Core Regulators of Proliferation in ER<sup>+</sup> Breast Cancer**  
David Endesfelder, Rebecca A. Burrell, Nnennaya Kanu, Nicholas McGranahan, Mike Howell, Peter J. Parker, Julian Downward, Charles Swanton, and Maik Kschischo

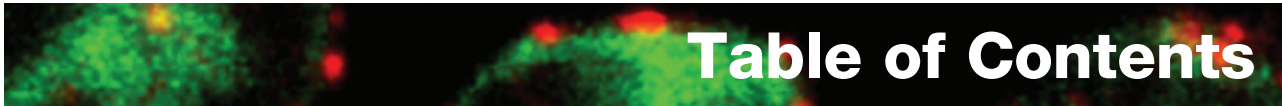
**Précis:** Chromosomal instability, a hallmark of cancer cells, permits a selection for gene copy number alternations in core regulators of proliferation that have prognostic value.

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- 4864 Epigenetic States of Cells of Origin and Tumor Evolution Drive Tumor-Initiating Cell Phenotype and Tumor Heterogeneity**  
Kin-Hoe Chow, Dong-Mi Shin, Molly H. Jenkins, Emily E. Miller, David J. Shih, Seungbum Choi, Benjamin E. Low, Vivek Philip, Brad Rybinski, Roderick T. Bronson, Michael D. Taylor, and Kyuson Yun  
*Précis:* This study probes the sources of tumor heterogeneity, a core research challenge that—despite its recognition by clinical pathologists for many years and its recent rediscovery by molecular geneticists—still represents the chief weakness of all cancer cell-targeted therapeutic strategies.
- 4875 TRIM29 Suppresses TWIST1 and Invasive Breast Cancer Behavior**  
Lingbao Ai, Wan-Ju Kim, Merve Alpay, Ming Tang, Carolina E. Pardo, Shigetsugu Hatakeyama, W. Stratford May, Michael P. Kladde, Coy D. Heldermon, Erin M. Siegel, and Kevin D. Brown  
*Précis:* TRIM29 exerts complex roles in cancer, but in breast cancer it appears to function as a tumor suppressor by suppressing a core regulator of the epithelial–mesenchymal transition, a pivotal step in driving invasive and metastatic behavior.
- 4888 TRIB1 Supports Prostate Tumorigenesis and Tumor-Propagating Cell Survival by Regulation of Endoplasmic Reticulum Chaperone Expression**  
Tetsuo Mashima, Taeko Soma-Nagae, Toshiro Migita, Ryoko Kinoshita, Atsushi Iwamoto, Takeshi Yuasa, Junji Yonese, Yuichi Ishikawa, and Hiroyuki Seimiya  
*Précis:* Prostate cancer stem-like cells appear to be addicted to oncogenic signals from an endoplasmic reticulum-dependent stress response pathway, a finding with potential therapeutic implications.
- 4898 IDH1 R132H Mutation Generates a Distinct Phospholipid Metabolite Profile in Glioma**  
Morteza Esmaeili, Bob C. Hamans, Anna C. Navis, Remco van Horssen, Tone F. Bathen, Ingrid S. Gribbestad, William P. Leenders, and Arend Heerschap  
*Précis:* This study reports novel noninvasive biomarkers of IDH-mutant gliomas that may help to guide treatments to target aberrant metabolism in these aggressive brain tumors.
- 4908 IL15RA Drives Antagonistic Mechanisms of Cancer Development and Immune Control in Lymphocyte-Enriched Triple-Negative Breast Cancers**  
Pierfrancesco Marra, Sumi Mathew, Anita Grigoriadis, Yin Wu, Fernanda Kyle-Cezar, Johnathan Watkins, Mamunur Rashid, Emanuele De Rinaldis, Sonya Hessey, Patrycja Gazinska, Adrian Hayday, and Andrew Tutt  
*Précis:* Expression of an immune memory-inducing receptor in some triple-negative breast cancers, usually only expressed by T cells, may offer a mechanistic explanation for the paradoxical association of some of these high-grade tumors with better survival outcomes.
- 4922 Epigenetic Targeting of Ovarian Cancer Stem Cells**  
Yinu Wang, Horacio Cardenas, Fang Fang, Salvatore Condello, Pietro Taverna, Matthew Segar, Yunlong Liu, Kenneth P. Nephew, and Daniela Matei  
*Précis:* These results suggest that epigenome-targeting strategies can reprogram residual cancer stem-like cells to a differentiated state, thereby helping prevent the development of recurrent, chemoresistant disease.
- 4937 Live-Cell Imaging of Invasion and Intravasation in an Artificial Microvessel Platform**  
Andrew D. Wong and Peter C. Searson  
*Précis:* An artificial microvessel platform can be used to obtain striking images and mechanistic insights into how cancer cells invade the local microenvironment and enter and exit vessels, providing a new tool to help unravel the complexities of metastasis and its prevention and treatment.

## LETTERS TO THE EDITOR

- 4946 A Synthetic Lethality-Based Strategy to Treat Cancers Harboring a Genetic Deficiency in the Chromatin Remodeling Factor BRG1—Letter**  
Kenneth W. Thompson, Stefanie B. Marquez, and David Reisman
- 4948 Proposal for a Synthetic Lethality Therapy Using the Paralog Dependence of Cancer Cells—Response**  
Takahiro Oike, Hideaki Ogiwara, Takashi Nakano, and Takashi Kohno



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## CORRECTIONS

**4950** Correction: The TGF $\beta$ -miR200-Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors

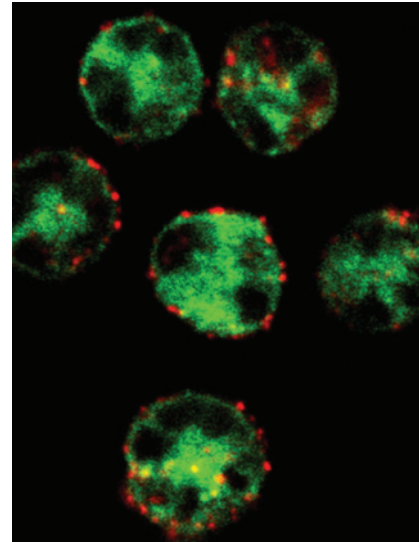
**4951** Correction: Chk2 Phosphorylation of Survivin- $\Delta$ Ex3 Contributes to a DNA Damage-Sensing Checkpoint in Cancer

 AC icon indicates Author Choice

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## ABOUT THE COVER

Confocal microscopy analysis for osteopontin performed on myeloid-derived suppressor cells (MDSC) shows osteopontin (red) localized under the cellular membrane but not colocalized with the ER marker concanavalin A (green) in MDSC. This picture is suggestive of the existence of an intracellular form, rather than a secreted form of osteopontin, in MDSC. For details, see article by S. Sangaletti and colleagues on page 4706.



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

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