


## BREAKING ADVANCES

- 5439** Highlights from Recent Cancer Literature

## REVIEWS

- 5441** Cancer Self-Defense: An Immune Stealth  
Kosei Nakajima, Pratima Nangia-Makker, Victor Hogan, and Avraham Raz
- 5445** The Rac GTPase in Cancer: From Old Concepts to New Paradigms  
Marcelo G. Kazanietz and Maria J. Caloca

## MOLECULAR AND CELLULAR PATHOBIOLOGY

- 5452** HIF-2 $\alpha$  Promotes Dissemination of Plasma Cells in Multiple Myeloma by Regulating CXCL12/CXCR4 and CCR1  
Kate Vandyke, Mara N. Zeissig, Duncan R. Hewett, Sally K. Martin, Krzysztof M. Mrozik, Chee Man Cheong, Peter Diamond, L. Bik To, Stan Gronthos, Daniel J. Peet, Peter I. Croucher, and Andrew C.W. Zannettino  
*Précis:* Chemokine receptor CCR1 is central to the process of dissemination of malignant plasma cells, a major cause of death in myeloma patients.
- 5464** STRAP Promotes Stemness of Human Colorectal Cancer via Epigenetic Regulation of the NOTCH Pathway  
 Lin Jin, Trung Vu, Guandou Yuan, and Pran K. Datta  
*Précis:* These findings identify a novel function for the signaling scaffold molecule STRAP as an activator of the NOTCH1-HES1 pathway that regulates cancer stem-like cells in colorectal cancer, with potential implications for prognosis and therapy.
- 5479** LSD1-Mediated Epigenetic Reprogramming Drives CENPE Expression and Prostate Cancer Progression  
Yi Liang, Musaddeque Ahmed, Haiyang Guo, Fraser Soares, Junjie T. Hua, Shuai Gao, Catherine Lu, Christine Poon, Wanting Han, Jens Langstein, Muhammad B. Ekram, Brian Li, Elai Davicioni, Mandeep Takhar, Nicholas Erho, R. Jeffrey Karnes, Dianne Chadwick, Theodoros van der Kwast, Paul C. Boutros, Cheryl H. Arrowsmith, Felix Y. Feng, Anthony M. Joshua, Amina Zoubeidi, Changmeng Cai, and Housheng H. He  
*Précis:* This study identified an important epigenetic driver and a promising therapeutic target of castration-resistant prostate cancer.

- 5491** Human Pluripotent Stem Cell-Derived TSC2-Haploinsufficient Smooth Muscle Cells Recapitulate Features of Lymphangioliomyomatosis  
Lisa M. Julian, Sean P. Delaney, Ying Wang, Alexander A. Goldberg, Carole Doré, Julien Yockell-Lelièvre, Roger Y. Tam, Krinio Giannikou, Fiona McMurray, Molly S. Shoichet, Mary-Ellen Harper, Elizabeth P. Henske, David J. Kwiatkowski, Thomas N. Darling, Joel Moss, Arnold S. Kristof, and William L. Stanford  
*Précis:* The patient iPSC-derived stem cell-based model described in this study will illuminate pathophysiology and therapeutic possibilities in cancers driven by mTOR pathway dysregulation.

## TUMOR AND STEM CELL BIOLOGY

- 5503** De Novo Lipid Synthesis Facilitates Gemcitabine Resistance through Endoplasmic Reticulum Stress in Pancreatic Cancer  
Saber Tadros, Surendra K. Shukla, Ryan J. King, Venugopal Gunda, Enza Vernucci, Jaime Abrego, Nina V. Chaika, Fang Yu, Audrey J. Lazenby, Lyudmyla Berim, Jean Grem, Aaron R. Sasson, and Pankaj K. Singh  
*Précis:* Our studies demonstrate that inhibition of de novo lipid synthesis in pancreatic cancer cells can overcome the resistance against fluoropyrimidines such as gemcitabine, which are key constituents of pancreatic cancer chemotherapy, by inducing ER stress and decreasing the stemness of cancer cells.
- 5518** Sensitivity to BUB1B Inhibition Defines an Alternative Classification of Glioblastoma  
Eunjee Lee, Margaret Pain, Huairen Wang, Jacob A. Herman, Chad M. Toledo, Jennifer G. DeLuca, Raymund L. Yong, Patrick Paddison, and Jun Zhu  
*Précis:* These findings offer a mechanism-based classification framework to predict the clinical course and therapeutic responses of glioblastomas.
- 5530** Loss of Tumor Suppressor STAG2 Promotes Telomere Recombination and Extends the Replicative Lifespan of Normal Human Cells  
Zharko Daniloski and Susan Smith  
*Précis:* These findings reveal a mechanism in normal and premalignant cells that could prolong the period during which tumor-driving mutations can accumulate, thereby increasing risks of cancer.

# Table of Contents

**5543** Shrimp miR-S8 Suppresses the Stemness of Human Melanoma Stem-like Cells by Targeting the Transcription Factor YB-1

Fan Yang, Jun Wei, Song Zhang, and Xiaobo Zhang

*Précis:* These results illuminate a novel aspect of miRNA-mediated cross-species gene expression and its use in regulating cancer stem-like cells.

## THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

**5554** Adaptation to TKI Treatment Reactivates ERK Signaling in Tyrosine Kinase–Driven Leukemias and Other Malignancies

J. Kyle Bruner, Hayley S. Ma, Li Li, Alice Can Ran Qin, Michelle A. Rudek, Richard J. Jones, Mark J. Levis, Keith W. Pratz, Christine A. Pratilas, and Donald Small

*Précis:* These findings necessitate a reassessment of how drug efficacy is evaluated and suggest that adding a low-dose MEK inhibitor to existing tyrosine kinase inhibitor therapy may improve efficacy.

**5564** Therapeutic Targeting of the CBP/p300 Bromodomain Blocks the Growth of Castration-Resistant Prostate Cancer



Lingyan Jin, Jesse Garcia, Emily Chan, Cecile de la Cruz, Ehud Segal, Mark Merchant, Samir Kharbanda, Ryan Raisner, Peter M. Haverly, Zora Modrusan, Justin Ly, Edna Choo, Susan Kaufman, Maureen H. Beresini, F. Anthony Romero, Steven Magnuson, and Karen E. Gascoigne

*Précis:* These findings offer a preclinical proof of concept for small-molecule therapies to target the CBP/p300 bromodomain as a strategy to treat castration-resistant prostate cancer.

**5576** ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage

Lukas Perkhofner, Anna Schmitt, Maria Carolina Romero Carrasco, Michaela Ihle, Stephanie Hampp, Dietrich Alexander Ruess, Elisabeth Hessmann, Ronan Russell, André Lechel, Ninel Azoitei, Qiong Lin, Stefan Liebau, Meike Hohwieler, Hanibal Bohnenberger, Marina Lesina, Hana Algül, Laura Gieldon, Evelin Schröck, Jochen Gaedcke, Martin Wagner, Lisa Wiesmüller, Bence Sipos, Thomas Seufferlein, Hans Christian Reinhardt, Pierre-Olivier Frappart, and Alexander Kleger

*Précis:* These findings illuminate the pathobiology of ATM-mutated pancreatic cancers and offer a preclinical mechanistic rationale for the use of PARP and ATR inhibitors to improve treatment of these cancers.

**5591** Monocarboxylate Transporter MCT1 Promotes Tumor Metastasis Independently of Its Activity as a Lactate Transporter

Valéry L. Payen, Myriam Y. Hsu, Kristin S. Räddecke, Elisabeth Wyart, Thibaut Vazeille, Caroline Bouzin, Paolo E. Porporato, and Pierre Sonveaux

*Précis:* NF- $\kappa$ B activation by lactate transporter MCT1 independently of its transport activity may explain why its deletion but not its pharmacological inhibition can most effectively block spontaneous tumor metastasis.

**5602** Structurally Novel Antiestrogens Elicit Differential Responses from Constitutively Active Mutant Estrogen Receptors in Breast Cancer Cells and Tumors

Yuechao Zhao, Mary J. Laws, Valeria Sanabria Guillen, Yvonne Ziegler, Jian Min, Abhishek Sharma, Sung Hoon Kim, David Chu, Ben Ho Park, Steffi Oesterreich, Chengjian Mao, David J. Shapiro, Kendall W. Nettles, John A. Katzenellenbogen, and Benita S. Katzenellenbogen

*Précis:* These findings uncover the basis for endocrine therapy resistance in breast cancers containing the two most common constitutively active estrogen receptor mutations, enabling precision medicine to be tailored to the patient's unique cancer mutations.

**5614** Therapeutic Effects of XPO1 Inhibition in Thymic Epithelial Tumors



Fabio Conforti, Xu Zhang, Guanhua Rao, Tommaso De Pas, Yoko Yonemori, Jose Antonio Rodriguez, Justine N. McCutcheon, Raneen Rahhal, Anna T. Alberobello, Yisong Wang, Yu-Wen Zhang, Udayan Guha, and Giuseppe Giaccone

*Précis:* These results offer preclinical proof of concept for the clinical testing of a small-molecule inhibitor of the nuclear export regulator XPO1 for treating thymic epithelial tumors.

## MICROENVIRONMENT AND IMMUNOLOGY

**5628** Anti-Jagged Immunotherapy Inhibits MDSCs and Overcomes Tumor-Induced Tolerance

Rosa A. Sierra, Jimena Trillo-Tinoco, Eslam Mohamed, Lolie Yu, Bhagelu R. Achyut, Ali Arbab, Jennifer W. Bradford, Barbara A. Osborne, Lucio Miele, and Paulo C. Rodriguez

*Précis:* Preclinical findings support the application of antibody-mediated Jagged blockade as a therapeutic strategy to overcome CD8<sup>+</sup> T-cell suppression in tumors and to improve immunotherapy outcomes.

# Table of Contents

**5639**  **$\beta$ -Adrenergic Signaling in Mice Housed at Standard Temperatures Suppresses an Effector Phenotype in CD8<sup>+</sup> T Cells and Undermines Checkpoint Inhibitor Therapy**



Mark J. Bucsek, Guanxi Qiao, Cameron R. MacDonald, Thejaswini Giridharan, Lauren Evans, Brian Niedzwecki, Haichao Liu, Kathleen M. Kokolus, Jason W.-L. Eng, Michelle N. Messmer, Kristopher Attwood, Scott I. Abrams, Bonnie L. Hylander, and Elizabeth A. Repasky

*Précis:* This preclinical study defines an actionable environmental stress pathway that suppresses antitumor immune checkpoint responses.

**5652** **CD73 Promotes Resistance to HER2/ErbB2 Antibody Therapy**

Martin Turcotte, David Allard, Deepak Mittal, Yacine Bareche, Laurence Buisseret, Vinu José, Sandra Pommey, Vincent Delisle, Sherene Loi, Heikki Joensuu, Pirkko-Liisa Kellokumpu-Lehtinen, Christos Sotiriou, Mark J. Smyth, and John Stagg

*Précis:* Targeting the cell surface AMP ectonucleotidase CD73 enhances anticancer responses induced by anti-HER2 therapy.

**5664** **GSK3 Inhibition Drives Maturation of NK Cells and Enhances Their Antitumor Activity**

Frank Cichocki, Bahram Valamehr, Ryan Bjordahl, Bin Zhang, Betsy Rezner, Paul Rogers, Svetlana Gaidarova, Stacey Moreno, Katie Tuininga, Phillip Dougherty, Valarie McCullar, Peter Howard, Dhifaf Sarhan, Emily Taras, Heinrich Schlums, Stewart Abbot, Daniel Shoemaker, Yenan T. Bryceson, Bruce R. Blazar, Scott Wolchko, Sarah Cooley, and Jeffrey S. Miller

*Précis:* This paper reveals how GSK3 kinase inhibitors can greatly enhance the characteristics of NK cells most desired for effective cancer immunotherapy, as applied for adoptive transfer in cancer patients with diverse types of malignancy.

**5676** **T Cells Deficient in Diacylglycerol Kinase  $\zeta$  Are Resistant to PD-1 Inhibition and Help Create Persistent Host Immunity to Leukemia**

Weiqing Jing, Jill A. Gershan, Sandra Holzhauer, James Weber, Katie Palen, Laura McOlash, Kirthi Pulakanti, Erin Wesley, Sridhar Rao, Bryon D. Johnson, and Matthew J. Riese

*Précis:* This study suggests that blocking the T-cell kinase diacylglycerol kinase  $\zeta$  may enhance the efficacy of adoptive cell and immune checkpoint therapies in cancer.

## CLINICAL STUDIES

**5687** **Phenotypic Heterogeneity of Circulating Tumor Cells Informs Clinical Decisions between AR Signaling Inhibitors and Taxanes in Metastatic Prostate Cancer**



Howard I. Scher, Ryon P. Graf, Nicole A. Schreiber, Brigit McLaughlin, Adam Jendrisak, Yipeng Wang, Jerry Lee, Stephanie Greene, Rachel Krupa, David Lu, Pascal Bamford, Jessica E. Louw, Lyndsey Dugan, Hebert A. Vargas, Martin Fleisher, Mark Landers, Glenn Heller, and Ryan Dittamore

*Précis:* This important study reports the use of circulating tumor cells to define a quantitative biomarker of tumor heterogeneity within an individual patient that can guide the choice of systemic treatment for metastatic castration-resistant prostate cancer.

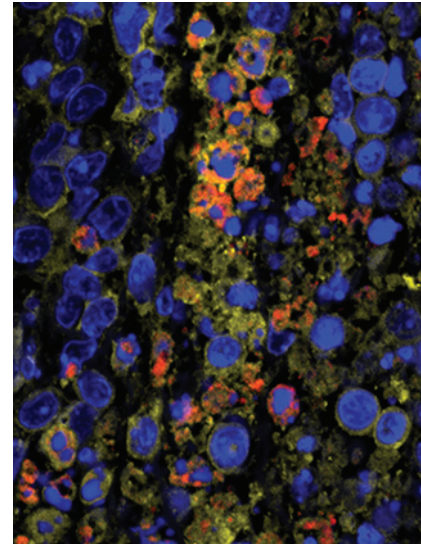
 AC icon indicates Author Choice

For more information please visit [www.aacrjournals.org](http://www.aacrjournals.org)

# Table of Contents

## ABOUT THE COVER

The double staining of intracytoplasmic cytoskeleton cytochromes and cleaved caspase-3 is a useful methodology to visualize cell death-related processes in tumors. Using immunofluorescence and confocal microscopy acquisition, it was found that treatment of EL-4 thymoma-bearing mice with a humanized antibody that recognizes Jagged 1 and 2 results in the coexpression of pan-cytokeratin (yellow) and cleaved caspase-3 (red) in the tumor. For details, see article by Sierra and colleagues on page 5628.



# Cancer Research

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

**77 (20)**

*Cancer Res* 2017;77:5439-5698.

**Updated version** Access the most recent version of this article at:  
<http://cancerres.aacrjournals.org/content/77/20>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/77/20>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.