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-2α 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, L. Bik To, Stan Grunthos, 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.

5456 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, Eli Davicioni, Mandeer Tahkar, Nicholas Erho, R. Jeffrey Karnes, Dianne Chadwick, Theodorus van der Kwaast, Paul C. Boutros, Cheryl H. Arrowsmith, Felix Y. Feng, Anthony M. Joshua, Amina Zoubidi, 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 Lymphangioleiomyomatosis
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
Précis: Our studies demonstrate that inhibition of de novo lipid synthesis in pancreatic cancer cells can overcome the resistance against fluopyrimidines 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, Huaien 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
Zbarko 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.
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. Haverty, 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.

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, Jed Min, Abhishek Sharma, Sung Hoon Kim, David Chu, Ben Ho Park, Steffi Oesterreich, Chengjian Mao, David J. Shaprio, Kendall W. Netteles, 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.

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


Précis: Preclinical findings support the application of antibody-mediated jagged blockade as a therapeutic strategy to overcome CD8+ T-cell suppression in tumors and to improve immunotherapy outcomes.
5639 β-Adrenergic Signaling in Mice Housed at Standard Temperatures Suppresses an Effector Phenotype in CD8^+ T Cells and Undermines Checkpoint Inhibitor Therapy

Mark J. Bucsek, Guanxi Qiao, Cameron R. MacDonald, Thijaswini Giridharan, Lauren Evans, Brian Niedzwiecki, Haichao Liu, Kathleen M. Kokolus, Jason W.-L. Eng, Michelle N. Messmer, Kristopher Atwood, 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 Buissneret, Vinu José, Sandra Pommey, Vincent Delisle, Sherene Loi, Heikki Jornsuu, Pirkko-Lisa 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 Abbott, Daniel Shoemaker, Yenam 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 ζ Are Resistant to PD-1 Inhibition and Help Create Persistent Host Immunity to Leukemia

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

Précis: This study suggests that blocking the T-cell kinase diacylglycerol kinase ζ 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.
ABOUT THE COVER

The double staining of intracytoplasmic cytoskeleton cytokeratins 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.