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, 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, Elia Davicioni, Mandeep Takhar, Nicholas Erho, R. Jeffrey Barnes, Dianne Chadwick, Theodorus van der Kwaast, 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.

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 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, Hauien Wang, Jacob A. Herman, Chad M. Toledo, Jennifer G. Deluca, Raymund L. Yong, Patrick Padison, 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.
Shrimp miR-S8 Suppresses the Stemness of Human Melanoma Stem-like Cells by Targeting the Transcription Factor YB-1

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

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

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.

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

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.

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

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.

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

Précis: NF-κB 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.

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

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.

Therapeutic Effects of XPO1 Inhibition in Thymic Epithelial Tumors

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.

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.
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, Thejaswini Giridharan, Lauren Evans, Brian Niedzwiecki, 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.

CD73 Promotes Resistance to HER2/ErbB2 Antibody Therapy
Martin Turcotte, David Allard, Deepak Mittal, Yacine Bareche, Laurence Buisset, Vina Joué, Sandra Pompey, Vincent Delisle, Sherene Loi, Heikki Joensuu, Pirikko-Lisa Kellokumpu-Lehtinen, Christos Sotiropou, Mark J. Smyth, and John Stagg

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

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, Yenan T. Byceson, 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.

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. Gershon, Sandra Holzhauer, James Weber, Katie Palen, Laura McOlash, Kirthi Pulakanti, Erin Wesley, Siddharth 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.

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 Jedresik, Yipeng Wang, Jerry Lee, Stephanie Greene, Rachel Krupa, David Lu, Pascal Bambord, 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.