BREAKING ADVANCES

1623 Highlights from Recent Cancer Literature

REVIEWS

1625 Contributions of the Host Microenvironment to Cancer-Induced Bone Disease
Sam W.Z. Olechowicz and Claire M. Edwards

1632 Optimization of Natural Killer T Cell–Mediated Immunotherapy in Cancer Using Cell-Based and Nanovector Vaccines
C. Faveeuw and F. Trottein

1639 Noncanonical Functions of Telomerase: Implications in Telomerase-Targeted Cancer Therapies
Yinghui Li and Vinay Tergaonkar

PRIORITY REPORTS

1645 Universal Marker and Detection Tool for Human Sarcoma Circulating Tumor Cells
Précis: This study describes the first universal and specific marker to detect circulating sarcoma cells in the blood, with the capability to detect any type of sarcoma, offering a key prognostic tool to monitor cancer metastasis and relapse in sarcoma patients.

1651 PCAT-1, a Long Noncoding RNA, Regulates BRCA2 and Controls Homologous Recombination in Cancer
John R. Prensner, Wei Chen, Matthew K. Iyer, Qi Cao, Teng Ma, Sumin Han, Anirban Sahu, Rohit Malik, Karri Wilder-Romans, Nora Navone, Christopher J. Logothetis, John C. Araujo, Li Zhuang, Dos D. Sarbassov, Li Ma, and Boyi Gan
Précis: A transcription factor that functions in tumor suppression was unexpectedly found to instead promote renal tumor growth under conditions of PI3K–AKT inhibition, with implications on how to improve antitumor responses.

1661 Cancer-Associated Mutations in Healthy Individuals: Assessing the Risk of Carcinogenesis
Ignacio A. Rodriguez-Brenes, Natalia L. Komarova, and Dominik Wodarz
Précis: Understanding how limits on cellular replication influence the fate of altered but nonneoplastic cells in healthy tissue may make it possible to estimate the risk posed by cancer-associated mutations found in healthy individuals.

INTEGRATED SYSTEMS AND TECHNOLOGIES

1670 Identification of Immune Factors Regulating Antitumor Immunity Using Polymeric Vaccines with Multiple Adjuvants
Omar A. Ali, Catia Verbeke, Chris Johnson, R. Warren Sands, Sarah A. Lewin, Des White, Edward Doherty, Glenn Dranoff, and David J. Mooney
Précis: This paper utilizes a new method to identify immune components critical to the efficacy of antitumor immune responses to tumors.

MICROENVIRONMENT AND IMMUNOLOGY

1682 FoxO Transcription Factors Promote AKT Ser473 Phosphorylation and Renal Tumor Growth in Response to Pharmacologic Inhibition of the PI3K–AKT Pathway
Aifu Lin, Hai-long Piao, Li Zhuang, Dos D. Sarbassov, Li Ma, and Boyi Gan
Précis: A transcription factor that functions in tumor suppression was unexpectedly found to instead promote renal tumor growth under conditions of PI3K–AKT inhibition, with implications on how to improve antitumor responses.

1694 Immune Escape and Survival Mechanisms in Circulating Tumor Cells of Colorectal Cancer
Gunnar Steinert, Sebastian Scholch, Thomas Niemietz, Naoki Iwata, Sebastian A. García, Bianca Behrens, Anita Voigt, Matthias Kloer, Axel Benner, Ulrich Bork, Nuh N. Rahbari, Markus W. Buchler, Nikola H. Stoecklein, Jurgen Weitz, and Moritz Koch
Précis: These results show that circulating colon tumor cells are genetically different from the primary colon tumor, exhibiting an immunosuppressive phenotype that enables them to evade immune eradication.
1705  UTX and MLL4 Coordinately Regulate Transcriptional Programs for Cell Proliferation and Invasiveness in Breast Cancer Cells

Jae-Hwan Kim, Amrish Sharma, Shilpa S. Dhar, Sung-Hun Lee, Bingnan Gu, Chia-Hsin Chan, Hui-Kuan Lin, and Min Gyu Lee

Précis: These findings show how coordinated regulation of gene expression programs by two distinct epigenetic modifiers drives malignant properties in breast cancer cells.

1718  Neuroplastic Changes Occur Early in the Development of Pancreatic Ductal Adenocarcinoma

Rachelle E. Stopczynski, Daniel P. Normolle, Douglas J. Hartman, Haoqiang Ying, Jennifer J. DeBerry, Klaus Bielefeldt, Andrew D. Rhim, Ronald A. DePinho, Kathryn M. Albers, and Brian M. Davis

Précis: These studies show that changes in the peripheral nervous system occur early during tumor development and may play an important role in disease progression.

1728  HDAC2 Provides a Critical Support to Malignant Progression of Hepatocellular Carcinoma through Feedback Control of mTORC1 and AKT

Ji Heon Oh, Hyun Jin Bae, Jung Woo Eun, Qingyu Shen, Se Jin Park, Hyung Seok Kim, Boas Nam, Woo Chan Shin, Eun Kyung Lee, Kyungbun Lee, Ja-Jun Jang, Won Sang Park, Jung Young Lee, and Suk Woo Nam

Précis: This study of a histone deacetylase that is essential for mitogenic signaling in liver cancers may offer a new interventional target for more effective therapy.

1739  p16INK4A Impairs Homologous Recombination–Mediated DNA Repair in Human Papillomavirus–Positive Head and Neck Tumors

Ruveyda Dök, Peter Kalev, Evert Jan Van Limbergen, Layka Abbasi Ashaghy, Iria Vázquez, Esther Hauben, Anna Sablina, and Sandra Nuyts

Précis: These findings reveal an unexpected function of the tumor suppressor p16INK4A in promoting the homologous recombination pathway of DNA repair, suggesting that p16INK4A status in head and neck cancer patients may offer an independent marker to predict their response to radiotherapy.

1752  Genetic Validation of the Protein Arginine Methyltransferase PRMT5 as a Candidate Therapeutic Target in Glioblastoma


Précis: This study presents a novel candidate prognostic and therapeutic target in aggressive brain cancers, with implications for understanding the basis for poor patient survival.

1766  Activated ERBB2/HER2 Licenses Sensitivity to Apoptosis upon Endoplasmic Reticulum Stress through a PERK-Dependent Pathway

Rosa Martín-Pérez, Carmen Palacios, Rosario Yerbes, Ana Cano-González, Daniel Iglesias-Serret, Joan Gil, Mauricio J. Reginato, and Abelardo López-Rivas

Précis: These findings offer a rationale for the therapeutic exploration of treatments inducing ER stress against mutant ERBB2-expressing breast tumor cells.

1778  ATDC/TRIM29 Phosphorylation by ATM/MAPKAP Kinase 2 Mediates Radiosensitivity in Pancreatic Cancer Cells

Lidong Wang, Huibin Yang, Phillip L. Palmbos, Gina Nef, Taylor Ann Deitzler, Dawn Coleman, Jacob Leflein, Mary Davis, Min Zhang, Wenhua Tang, J. Kevin Hicks, Corey M. Helchowski, Jayendra Prasad, Theodore S. Lawrence, Liang Xu, Xiaochun Yu, Christine E. Canman, Mats Ljungman, and Diane M. Simeone

Précis: These findings link a TRIM family protein that binds DNA and p53 to radiosensitivity in pancreatic cancer, suggesting its candidacy as a therapeutic target to improve the efficacy of DNA-damaging treatments used to treat this disease.
Alarmin IL-33 Acts as an Immunoadjuvant to Enhance Antigen-Specific Tumor Immunity
Daniel O. Villarreal, Megan C. Wise, Jewell N. Walters, Emma L. Reuschel, Min Joung Choi, Nyamekye Obeng-Adjei, Jian Yan, Matthew P. Morrow, and David B. Weiner

miR-30-5p Functions as a Tumor Suppressor and Novel Therapeutic Tool by Targeting the Oncogenic Wnt/β-Catenin/BCL9 Pathway
Jian-Jun Zhao, Jianhong Lin, Di Zhu, Xujun Wang, Daniel Brooks, Ming Chen, Zhang-Bo Chu, Kohichi Takada, Bryan Ciccarelli, Samir Admin, J ianguo Tao, Yu-Tzu Tai, Steven Teoon, Geraldine Pinkus, Winston Patrick Kuo, Teru Hideshima, Mary Bouxsein, Nikhil Munshi, Kenneth Anderson, and Ruben C arrasco

Sox2 Is Required to Maintain Cancer Stem Cells in a Mouse Model of High-Grade Oligodendroglia
Rebecca Favaro, Irene Appolloni, Serena Pellegratta, Alexandra Badiola Sangà, Pierfrancesco Pagella, Eleonora Gambini, Federica Pisati, Sergio Ottolenghi, Maria Foti, Gaetano Finocchiaro, Paolo Malatesta, and Silvia K. Nicola

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Jian-Jun Zhao, Jianhong Lin, Di Zhu, Xujun Wang, Daniel Brooks, Ming Chen, Zhang-Bo Chu, Kohichi Takada, Bryan Ciccarelli, Samir Admin, Jianguo Tao, Yu-Tzu Tai, Steven Teoon, Geraldine Pinkus, Winston Patrick Kuo, Teru Hideshima, Mary Bouxsein, Nikhil Munshi, Kenneth Anderson, and Ruben Carrasco

Précis: These findings offer a preclinical proof of concept that IL-33 improves the immune potency of tumor vaccines, promoting tumor cell clearance and regressions to fully empower cancer immunotherapy.

Expression of Variant Isoforms of the Tyrosine Kinase SYK Determines the Prognosis of Hepatocellular Carcinoma
Jian Hong, Yunfei Yuan, Jianping Wang, Yadi Liao, Ruhai Zou, Chuanlong Zhu, Binkui Li, Yi Liang, Pinzhu Huang, Zongwei Wang, Wenyu Lin, Yixin Zeng, Jia Le Dai, and Raymond T. Chung

Précis: These findings define opposing functions of the two isoforms of the SYK kinase in liver cancer, with the larger isoform enhancing invasion and the smaller isoform enhancing metastasis, patterns that in patient specimens offer strong predictors of overall survival.

TUMOR AND STEM CELL BIOLOGY

Chromosome 10, Frequently Lost in Human Melanoma, Encodes Multiple Tumor-Suppressive Functions
Lawrence N. Kwong and Lynda Chin

Précis: These results show how regional aberrations in chromosome copy number can lead to loss of multiple important tumor-suppressor functions in cancer.

Id2 Mediates Oligodendrocyte Precursor Cell Maturation Arrest and Is Tumorigenic in a PDGF-Rich Microenvironment
Matthew C. Havrda, Brenton R. Paoliella, Cong Ran, Karola S. Jering, Christina M. Wray, Jaclyn M. Sullivan, Audrey Nailor, Yasuyuki Hitoshi, and Mark A. Israel

Précis: This study of distinct subsets of adult tissue progenitors points to a maturation arrest of oligodendroglial precursor cells in the pathogenesis of PDGF-dependent brain tumors.
CORRECTION

1881 Correction: EPR Oxygen Images Predict Tumor Control by a 50% Tumor Control Radiation Dose

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ABOUT THE COVER

Pancreas from a 12-week-old KPCT (p48-Cre; LSL-KrasG12D; p53flop/++; Rosa26-LSL-tdTomato) mouse with precancerous PanIN lesions but no tumor. dtTomato-label (red) marks pancreas epithelial-derived cells, in this case normal-appearing acinar cells. PGP 9.5 antibody (green) was used to stain nerve fibers that exhibit hypertrophy and sprouting within pancreatic tissue, beginning at histologic precancer stages and increasing as the disease progresses. For details, see article by Stopczynski and colleagues on page 1718.