BREAKING ADVANCES

6793 Highlights from Recent Cancer Literature

REVIEWS

6795 Discovery of IDO1 Inhibitors: From Bench to Bedside
George C. Prendergast, William P. Malachowski, James B. DuHadaway, and Alexander J. Muller

6812 Emerging Role of CRISPR/Cas9 Technology for MicroRNAs Editing in Cancer Research
Guillermo Aquino-Jarquin

PRIORITY REPORT

6818 RUNX1 Upregulation by Cytotoxic Drugs Promotes Apoptosis
Daniel Speidel, Jasmin Wellbrock, and Melissa Abas
Précis: These findings reveal a proapoptotic function for a gene primarily known as a differentiation factor, offering a possible explanation for its association with drug resistance in leukemia.

MOLECULAR AND CELLULAR PATHOBIOLOGY

6825 PP2A Inactivation Mediated by PPP2R4 Haploinsufficiency Promotes Cancer Development
Ward Sents, Bob Meessen, Petar Kalev, Enrico Radaelli, Xavier Sagartz, Eline Miermans, Dorien Haesen, Caroline Lambrecht, Mieke Dewerchin, Peter Carmeliet, Jukka Westermarck, Anna Sablina, and Veerle Janssens
Précis: This seminal study defines a haploinsufficient tumor suppressor gene that provides a high-penetration mechanism for inhibition of the antioncogenic phosphatase PP2A in human cancer.

6838 SKP2 Activation by Thyroid Hormone Receptor β2 Bypasses Rb-Dependent Proliferation in Rb-Deficient Cells
Xiaoliang L. Xu, Zhengke Li, AiHong Liu, Xianqun Fan, Dan-ning Hu, Dong-Lai Qi, David W. Chitty, Renbing Jia, Jianping Qui, Justin Q. Wang, Jake Sharaf, Jun Zou, Rebecca Weiss, Hongyan Huang, Walter J. Joseph, Lily Ng, Richard Rosen, Binghui Shen, Mark W. Reid, Douglas Forrest, David H. Abramson, Samuel Singer, David Coblirnik, and Suresh C. Jhanwar
Précis: Sensitivity to germline RB1 mutations can be conferred by a cell type–restricted thyroid hormone receptor isoform that fulfills otherwise Rb-dependent cell-cycle and survival function.

6851 STK33 Promotes Growth and Progression of Pancreatic Cancer as a Critical Downstream Mediator of HIF1α
Fanyang Kong, Xiangyu Kong, Yiqi Du, Ying Chen, Xuan Deng, Jianwei Zhu, Jiawei Du, Lei Li, Zhiliang Jia, Dacheng Xie, Zhaoshen Li, and Keping Xie
Précis: These findings offer a preclinical proof of concept for targeting the serine/threonine kinase STK33 as a therapeutic approach to improve PDAC management.

6863 PACE4 Undergoes an Oncogenic Alternative Splicing Switch in Cancer
Frédéric Couture, Robert Sabbagh, Anna Kwiatkowska, Roxane Desjardins, Simon-Pierre Guay, Luigi Bouchard, and Robert Day
Précis: These findings identify the cellular mechanisms of a major nonandrogenic pathway that could be targeted to complement existing therapies in advanced prostate cancers.

6880 Protein Acyltransferase DHHC3 Regulates Breast Tumor Growth, Oxidative Stress, and Senescence
Chandan Sharma, Hong-Xing Wang, Qinglin Li, Konstantin Knoblich, Emily S. Reisenbichler, Andrea L. Richardson, and Martin E. Hemler
Précis: Through its palmitoylation activity, the protein acyltransferase DHHC3 negatively regulates oxidative stress, senescence, and immune surveillance in breast cancer.

6902 miR-6883 Family miRNAs Target CDK4/6 to Induce G1 Phase Cell-Cycle Arrest in Colon Cancer Cells
Amriti R. Lulla, Michael J. Slifker, Yan Zhou, Avital Lev, Margret B. Einarsen, David T. Dicker, and Wafik S. El-Deiry
Précis: These findings provide a rationale for use of miRNA mimics as adjuvant therapy for colorectal cancer.
SGK1 Is a Critical Component of an AKT-Independent Pathway Essential for PI3K-Mediated Tumor Development and Maintenance
Arturo Orlacchio, Michela Ranieri, Martina Brave, Valeria Antico Artich, Toni Forde, Daniela De Martino, Karen E. Anderson, Phillip Hawkins, and Antonio Di Cristofano

Précis: Targeting the AGC kinase SGK1 along with AKT inhibits proliferation of neoplastically transformed cells more efficiently than blocking both PI3K and AKT, a finding with potential implications for treating tumors with increased PI3K signaling.

TUMOR AND STEM CELL BIOLOGY

NFκB Promotes Ovarian Tumorigenesis via Classical Pathways That Support Proliferative Cancer Cells and Alternative Pathways That Support ALDH+ Cancer Stem–like Cells
Carrie D. House, Elizabeth Jordan, Lidia Hernandez, Michelle Ozaki, Jana M. James, Marianne Kim, Michael J. Kruhlik, Eric Batchelor, Fathi Elloumi, Margaret C. Cam, and Christina M. Annunziata

Précis: Classical and alternate NFκB signaling pathways sustain tumor-initiating cells in advanced ovarian cancer, with implications for improved understanding of disease recurrence.

Mitochondrial Haplotype Alters Mammary Cancer Tumorigenicity and Metastasis in an Oncogenic Driver–Dependent Manner
Amanda E. Brinker, Carolyn J. Vivian, Devin C. Koestler, Trevor T. Tsue, Roy A. Jensen, and Danny R. Welch

Précis: These seminal findings show that the influence of mitochondrial genetics on cancer metastasis occurs in conjunction with oncogenic drivers.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Blocking Myristoylation of Src Inhibits Its Kinase Activity and Suppresses Prostate Cancer Progression
Sungjin Kim, Omar Awad Alsaidan, Octavia Goodwin, Qianjin Li, Esthelo Suliejami, Zhen Han, Aiping Bai, Thomas Albers, Zdenka Beharry, Y. George Zheng, Jonathan T. Goldstein, Ashton C. Berger, Juliann Shih, Goktug Celiker, Laura Furst, David J. Kwiatkowski, Andrew D. Cherniack, Matthew Meyerson, and Craig A. Strathdee

Précis: These results offer preclinical proof of concept for a selective FGFR-4 inhibitor as a candidate therapeutic target in bladder cancer.

New Generation Nanomedicines Constructed from Self-Assembling Small-Molecule Prodrugs Alleviate Cancer Drug Toxicity
Hangxiang Wang, Zhongjie Lu, Liang Wang, Tingsheng Guo, Iaping Wu, Jianqin Wan, Liqian Zhou, Hui Li, Zhen Li, Donghai Jiang, Penghong Song, Haiyang Xie, Lin Zhou, Xiao Xu, and Shunen Zheng

Précis: This report offers an innovative scalable strategy for generating stable and better tolerated cytotoxic nanomedicines.

Genomic Activation of PPARG Reveals a Candidate Therapeutic Axis in Bladder Cancer
Jonathan T. Goldstein, Ashton C. Berger, Juliann Shih, Goktug Celiker, Laura Furst, David J. Kwiatkowski, Andrew D. Cherniack, Matthew Meyerson, and Craig A. Strathdee

Précis: These results offer a preclinical proof of concept for a nuclear receptor PPARG as a candidate therapeutic target in bladder cancer.

H3B-6527 Is a Potent and Selective Inhibitor of FGFR4 in FGF19-Driven Hepatocellular Carcinoma
Jaya Julie Joshi, Heather Coffey, Erik Corcoran, Jennifer Tsai, Chia-Ling Huang, Kana Ichikawa, Sudeep Prajapati, Ming-Hong Hao, Suzanna Bailey, Jeremy Wu, Victoria Rimkunas, Craig Karr, Vanitha Subramanian, Pavan Kumar, Crystal MacKenzie, Raelene Hurley, Takashi Satoh, Kun Yu, Eunice Park, Nathalie Rious, Amy Kim, Weidong G. Lai, Lihua Yu, Ping Zhu, Silvia Buonamici, Nicholas Larsen, Peter Fekkes, John Wang, Markus Warmuth, Dominic J. Reynolds, Peter G. Smith, and Anand Selvaraj

Précis: These results offer a preclinical proof of concept for a selective FGFR-4 inhibitor as a candidate therapeutic agent to treat liver cancers that exhibit increased expression of FGF19, including in effective combinations with the CDK4/6 inhibitor palbociclib.
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7049  A Synthetic CD8α:MyD88 Coreceptor Enhances CD8+ T-cell Responses to Weakly Immunogenic and Lowly Expressed Tumor Antigens
Sabina Kaczanowska, Ann Mary Joseph, Jiashao Guo, Alexander K Tsai, Jackline Joy Lasola, Renisha Younger, Yuji Zhang, Cruz Velasco Gonzales, and Eduardo Davila
Précis: These findings highlight a unique method to lower the T-cell receptor recognition threshold to any antigen and the ability to reshape the tumor environment to one that favors antitumor immunity independent of HLA type.

7059  Restoration of Natural Killer Cell Antimetastatic Activity by IL12 and Checkpoint Blockade
Isabel Ohs, Laura Ducimetiere, Joana Marinho, Paulina Kulig, Burkhard Becher, and Sonia Tugues
Précis: These findings extend understanding of the mechanism of action of immune checkpoint therapy by broadening its targets beyond T cells to include natural killer cells, an innate arm of antitumor immunity.

7072  Paxillin Binding to the Cytoplasmic Domain of CD103 Promotes Cell Adhesion and Effector Functions for CD8+ Resident Memory T Cells in Tumors
Ludiane Gauthier, Stéphanie Corgnac, Marie Boutet, Gwendoline Gros, Pierre Validire, Georges Bismuth, and Fathia Mami-Chouaib
Précis: These findings identify a signaling event required for functional activities of an intratumoral class of memory T cells, with implications for the success of T-cell-based immunotherapies for cancer.

7083  Emergence of High-Avidity Melan-A–Specific Clonotypes as a Reflection of Anti–PD-1 Clinical Efficacy
Sylvain Simon, Virginie Vignard, Emilie Varey, Tiphaïne Parrot, Anne-Chantal Knol, Amir Khammari, Nadine Gervois, Francois Lang, Brigitte Dreno, and Nathalie Labarriere
Précis: These results suggest a candidate surrogate marker that may predict positive antitumor responses to anti-PD-1 therapy, addressing a question of great clinical interest.

7094  TLR4-Mediated Inflammation Promotes KSHV-Induced Cellular Transformation and Tumorigenesis by Activating the STAT3 Pathway
Marion Guffaz, Karthik Vasan, Brandon Tan, Suzane Ramos da Silva, and Shou-Jiang Gao
Précis: These findings suggest a complex relationship between infections, metabolic syndromes, and innate immune responses in patients who have AIDS-related Kaposi sarcoma, with implications for understanding how the immune system attacks cancers or fails to do so.

7109  Distinct Angiogenic Changes during Carcinogenesis Defined by Novel Label-Free Dark-Field Imaging in a Hamster Cheek Pouch Model
Fangyao Hu, Hannah Martin, Amy Martinez, Jeffrey Everitt, Alaaatnin Ekanli, Walter T. Lee, Mark Dewhirst, and Nimmi Ramamujam
Précis: A novel method to image neovascularization allows for extraction and analysis of specific vascular features for the purposes of cancer screening and prevention.
7120  [18F]Fluorothymidine PET Informs the Synergistic Efficacy of Capecitabine and Trifluridine/Tipiracil in Colon Cancer
Seog-Young Kim, Jin Hwa Jung, Haeng Jung Lee, Hyunsu Soh, Sang Ju Lee, Seung Jun Oh, Sun Young Chae, Jai Hyuen Lee, Seung Jin Lee, Yong Sang Hong, Tae Won Kim, and Dae Hyuk Moon
Précis: These findings suggest that any inhibitor with a primary target mechanism of thymidylate synthase inhibition may be combined with trifluridine/tipiracil in colon cancer and possibly other cancer types.

LETTER TO THE EDITOR

7131  A Systems Approach to Prostate Cancer Classification—Letter
Elin Thysell, Erik Bovinder Ylitalo, Emma Jernberg, Anders Bergh, and Pernilla Wikström

7133  A Systems Approach to Prostate Cancer Classification—Response
Sungyong You and Michael R. Freeman

CORRECTION

7136  Correction: JARID1B Enables Transit between Distinct States of the Stem-like Cell Population in Oral Cancers

7137  Acknowledgment to Reviewers

ABOUT THE COVER

Mitochondrial polymorphisms are associated with defining human clades (races) and with susceptibility to mammary tumor development and metastasis. Brinker and colleagues show that metastatic efficiency changes with different mitochondrial haplotypes in an oncogenic driver-dependent manner. Vimentin is a marker of an epithelial-mesenchymal transition, a process that is often associated with tumor invasion and metastasis. Unexpectedly, no effect on vimentin immunohistochemical staining was observed in HER2-driven mammary tumors despite changes in metastatic efficiency. For details, see article by Brinker and colleagues on page 6941.