

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 Meeusen, Petar Kalev, Enrico Radaelli, Xavier Sagaert, 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-penetrance mechanism for inhibition of the antioncogenic phosphatase PP2A in human cancer.

- 6838** SKP2 Activation by Thyroid Hormone Receptor β 2 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 Cobrinik, 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 HIF1 α

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.

- 6891** Subtype-Specific Tumor-Associated Fibroblasts Contribute to the Pathogenesis of Uterine Leiomyoma

Xin Wu, Vanida A. Serna, Justin Thomas, Wenan Qiang, Michael L. Blumenfeld, and Takeshi Kurita

Précis: Tumor-associated fibroblasts regulate smooth muscle cells containing MED12 mutations to drive development of uterine leiomyoma.

- 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. Einarson, 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.

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6914 **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 Arciuch, 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.

6963 **New Generation Nanomedicines Constructed from Self-Assembling Small-Molecule Prodrugs Alleviate Cancer Drug Toxicity**



Hangxiang Wang, Zhongjie Lu, Lijiang Wang, Tingting Guo, Jiaping Wu, Jianqin Wan, Liqian Zhou, Hui Li, Zhen Li, Donghai Jiang, Penghong Song, Haiyang Xie, Lin Zhou, Xiao Xu, and Shusen Zheng

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

TUMOR AND STEM CELL BIOLOGY

6927 **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.

6941 **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.

6975 **SOCS1 Gene Therapy Improves Radiosensitivity and Enhances Irradiation-Induced DNA Damage in Esophageal Squamous Cell Carcinoma**

Takahito Sugase, Tsuyoshi Takahashi, Satoshi Serada, Minoru Fujimoto, Kosuke Hiramatsu, Tomoharu Ohkawara, Koji Tanaka, Yasuhiro Miyazaki, Tomoki Makino, Yukinori Kurokawa, Makoto Yamasaki, Kiyokazu Nakajima, Tadamitsu Kishimoto, Masaki Mori, Yuichiro Doki, and Tetsuji Naka

Précis: This paper presents a mechanistic rationale for a strategy to improve the response of esophageal cancers to radiotherapy, which tends to be resistant to this modality.

6987 **Genomic Activation of PPARγ Reveals a Candidate Therapeutic Axis in Bladder Cancer**

Jonathan T. Goldstein, Ashton C. Berger, Juliann Shih, Fujiko F. Duke, 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 PPARγ as a candidate therapeutic target in bladder cancer.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

6950 **Blocking Myristoylation of Src Inhibits Its Kinase Activity and Suppresses Prostate Cancer Progression**

Sungjin Kim, Omar Awad Alsaidan, Octavia Goodwin, Qianjin Li, Essilvo Sulejmani, Zhen Han, Aiping Bai, Thomas Albers, Zanna Beharry, Y. George Zheng, James S. Norris, Zdzislaw M. Szulc, Alicja Bielawska, Iryna Lebedyeva, Scott D. Pegan, and Houjian Cai

Précis: These results offer preclinical proof of concept for the development of N-myristoyltransferase inhibitors as a therapeutic modality to improve the management of prostate cancer.

6999 **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 Rioux, 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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7014 ATR Is a Therapeutic Target in Synovial Sarcoma



Samuel E. Jones, Emmy D.G. Fleuren, Jessica Frankum, Asha Konde, Chris T. Williamson, Dragomir B. Krastev, Helen N. Pemberton, James Campbell, Aditi Gulati, Richard Elliott, Malini Menon, Joanna L. Selfe, Rachel Brough, Stephen J. Pettitt, Wojciech Niedzwiedz, Winette T.A. van der Graaf, Janet Shipley, Alan Ashworth, and Christopher J. Lord

Précis: Reliance of synovial sarcomas on the DNA damage signaling factor ATR underscores the mechanistic relevance of ATR inhibitors to treat this cancer, either as single-agent therapy or in combination with cisplatin or PARP inhibitors.

7027 Cathepsin B Is Dispensable for Cellular Processing of Cathepsin B-Cleavable Antibody-Drug Conjugates



Niña G. Caculitan, Josefa dela Cruz Chuh, Yong Ma, Donglu Zhang, Katherine R. Kozak, Yichin Liu, Thomas H. Pillow, Jack Sadowsky, Tommy K. Cheung, Qui Phung, Benjamin Haley, Byoung-Chul Lee, Robert W. Akita, Mark X. Sliwkowski, and Andrew G. Polson

Précis: The findings of this study challenge the assumed mechanism of action by which an antibody-drug conjugate releases its drug to achieve targeted cancer cell killing.

7038 MALT1 Inhibition Is Efficacious in Both Naïve and Ibrutinib-Resistant Chronic Lymphocytic Leukemia

Nakhle S. Saba, Deanna H. Wong, Georges Tanios, Jessica R. Iyer, Patricia Lobelle-Rich, Eman L. Dadashian, Delong Liu, Lorena Fontan, Erik K. Flemington, Cydney M. Nichols, Chingiz Underbayev, Hana Safah, Ari Melnick, Adrian Wiestner, and Sarah E. M. Herman

Précis: This important study shows how a small-molecule inhibitor of the paracaspase MALT1 could offer an effective strategy to treat chronic lymphocytic leukemias that become resistant to ibrutinib.

MICROENVIRONMENT AND IMMUNOLOGY

7049 A Synthetic CD8 α :MyD88 Coreceptor Enhances CD8⁺ T-cell Responses to Weakly Immunogenic and Lowly Expressed Tumor Antigens



Sabina Kaczanowska, Ann Mary Joseph, Jitao Guo, Alexander K Tsai, Jackline Joy Lasola, Kenisha 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 Ducimetière, 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, Tiphaine 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 Gruffaz, 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.

INTEGRATED SYSTEMS AND TECHNOLOGIES

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, Alaattin Erkanli, Walter T. Lee, Mark Dewhirst, and Nimmi Ramanujam

Précis: A novel method to image neovascularization allows for extraction and analysis of specific vascular features for the purposes of cancer screening and prevention.

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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

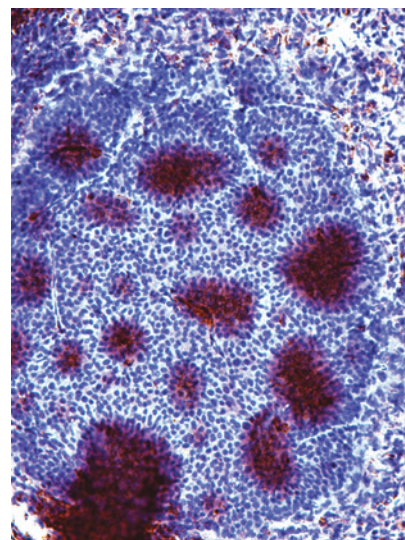
7137 Acknowledgment to Reviewers

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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.



Cancer Research

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