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

Precis: 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 Meusens, Petar Kaley, Enrico Radaelli, Xavier Sagraert, Eline Miermans, Petar Kaley, Enrico Radaelli, Xavier Sagraert, Eline Miermans, Dorien Haesen, Caroline Lambrecht, Mieke Dewerchin, Peter Carmeliet, Jukka Westermarck, Anna Sablina, and Veerle Janssens

Precis: 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 β2 Bypasses Rb-Dependent Proliferation in Rb-Deficient Cells

Precis: 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.

6880 Protein Acyltransferase DHHC3 Regulates Breast Tumor Growth, Oxidative Stress, and Senescence
Chandran Sharma, Hong-Xing Wang, Qinglin Li, Konstantin Knoblich, Emily S. Reisenbichler, Andrea L. Richardson, and Martin E. Hemler

Precis: 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

Precis: 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. Slater, Yan Zhou, Avital Lev, Margret B. Elnarson, David T. Dicker, and Wafik S. El-Deiry

Precis: These findings provide a rationale for use of miRNA mimics as adjuvant therapy for colorectal cancer.
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<td>SGK1 Is a Critical Component of an AKT-Independent Pathway Essential for PI3K-Mediated Tumor Development and Maintenance</td>
<td>Arturo Orlacchio, Michela Ranieri, Martina Brave, Valeria Antico Aricich, Toni Forde, Daniela De Martino, Karen E. Anderson, Phillip Hawkins, and Antonio Di Cristofano</td>
<td>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.</td>
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<td>6941</td>
<td>Mitochondrial Haplotype Alters Mammary Cancer Tumorigenicity and Metastasis in an Oncogenic Driver–Dependent Manner</td>
<td>Amanda E. Brinker, Carolyn J. Vivian, Devin C. Koestler, Trevor T. Tsue, Roy A. Jensen, and Danny R. Welch</td>
<td>Précis: These seminal findings show that the influence of mitochondrial genetics on cancer metastasis occurs in conjunction with oncogenic drivers.</td>
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<td>6950</td>
<td>Blocking Myristoylation of Src Inhibits Its Kinase Activity and Suppresses Prostate Cancer Progression</td>
<td>Sungjin Kim, Omar Awd AlSaidan, Octavia Goodwin, Qianxin Li, Eslivo Suljejmani, Zhen Han, Aiping Bai, Thomas Albers, Zannan Beharry, Y. George Zheng, James S. Norris, Zdzislaw M. Szule, Alicja Bielawska, Iryna Lebedyeva, Scott D. Pegan, and Houjian Cai</td>
<td>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.</td>
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<td>6967</td>
<td>SOCS1 Gene Therapy Improves Radiosensitivity and Enhances Irradiation-Induced DNA Damage in Esophageal Squamous Cell Carcinoma</td>
<td>Takahito Sugase, Tsuyoshi Takahashi, Satoshi Serada, Minoru Fujimoto, Koosuke Hiramatsu, Tomoharu Ohkawara, Koji Tanaka, Yasuhiro Miyazaki, Tomoki Makino, Yukinori Kurokawa, Makoto Yamazaki, Kiyokazu Nakajima, Tadamitsu Kishimoto, Manaki Mori, Yuichiro Doki, and Tetsuji Naka</td>
<td>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.</td>
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<td>6987</td>
<td>Genomic Activation of PPARG Reveals a Candidate Therapeutic Axis in Bladder Cancer</td>
<td>Jonathan T. Goldstein, Ashton C. Berger, Juliann Shih, Fujiko F. Duke, Laura Furst, David J. Kwaitkowsi, Andrew D. Cherniack, Matthew Meyerson, and Craig A. Strathdee</td>
<td>Précis: These results offer a preclinical proof of concept for a nuclear receptor PPARG as a candidate therapeutic target in bladder cancer.</td>
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<td>6999</td>
<td>H3B-6527 Is a Potent and Selective Inhibitor of FGFR4 in FGF19-Driven Hepatocellular Carcinoma</td>
<td>Jaya Julie Joshi, Heather Coffey, Erik Corcoran, Jennifer Tsai, Chia-Ling Huang, Kana Ichikawa, Sudeep Prajapati, Ming-Hong Hao, Suzanna Bailey, Jeremy Wu, Victoria Rinkunas, Craig Karr, Vanitha Subramamian, Pavan Kumar, Crystal MacKenzie, Raelene Hurley, Takashi Satoh, Kun Yu, Ennice 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</td>
<td>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.</td>
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ATR Is a Therapeutic Target in Synovial Sarcoma

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

Precis: 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

Precis: 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.

Restoration of Natural Killer Cell Antimetastatic Activity by IL.12 and Checkpoint Blockade
Isabel Ohs, Laura Ducimetiere, Joana Marinaho, Paulina Kulig, Burkhard Becher, and Sonia Tugues

Precis: 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.

7059 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 Cognauc, Marie Boutet, Gwendoline Gros, Pierre Validire, Georges Bismuth, and Fathia Mami-Chouaib

Precis: The 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.

7072 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

Precis: 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.

7083 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

Precis: 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.

7094 TLRA-Mediated Inflammation Promotes Tumors Defined by Novel Label-Free Dark-Field Imaging in a Hamster Cheek Pouch Model
Fangyao Hu, Hannah Martin, Amy Martinez, Jeffrey Everitt, Alaattin Ekanli, Walter T. Lee, Mark Dewhirst, and Nimmi Ramamujam

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

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

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

CORRECTION

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

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.