

BREAKING ADVANCES

- 4439** Highlights from Recent Cancer Literature


REVIEWS

- 4441** Plasticity beyond Cancer Cells and the "Immunosuppressive Switch"
Zvi Granot and Zvi G. Fridlender
- 4446** Tetracycline Antibiotics Impair Mitochondrial Function and Its Experimental Use Confounds Research
 Iliana A. Chatzisprou, Ntsiki M. Held, Laurent Mouchiroud, Johan Auwerx, and Riekelt H. Houtkooper

PRIORITY REPORTS

- 4450** YAP Promotes Malignant Progression of *Lkb1*-Deficient Lung Adenocarcinoma through Downstream Regulation of Survivin
Wenjing Zhang, Yijun Gao, Fuming Li, Xinyuan Tong, Yan Ren, Xiangkun Han, Shun Yao, Fei Long, Zhongzhou Yang, Hengyu Fan, Lei Zhang, and Hongbin Ji
Précis: These findings suggest a rationale for personalized therapeutic management of non-small cell lung cancers, which harbor *LKB1* mutations.
- 4458** NUP160–SLC43A3 Is a Novel Recurrent Fusion Oncogene in Angiosarcoma
Naoki Shimoazono, Masatoshi Jinnin, Mamiko Masuzawa, Mikio Masuzawa, Zhongzhi Wang, Ayaka Hirano, Yukiko Tomizawa, Tomomi Etoh-Kira, Ikko Kajihara, Miho Harada, Satoshi Fukushima, and Hironobu Ihn
Précis: These findings advance knowledge concerning the genetic causes of angiosarcoma, with potential implications for new diagnostic and therapeutic approaches.
- 4466** Glioblastomas Require Integrin $\alpha v\beta 3$ /PAK4 Signaling to Escape Senescence
Aleksandra Franovic, Kathryn C. Elliott, Laetitia Seguin, M. Fernanda Camargo, Sara M. Weis, and David A. Cheresh
Précis: Glioblastomas are selectively addicted to a pathway that helps them evade oncogene-induced senescence, with implications for novel therapeutic opportunities to target this aggressive form of brain cancer.

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 4474** Urokinase Exerts Antimetastatic Effects by Dissociating Clusters of Circulating Tumor Cells
 Jin Woo Choi, Jun Ki Kim, Yun Jung Yang, Pilhan Kim, Kwon-Ha Yoon, and Seok Hyun Yun
Précis: This important study offers a preclinical proof of concept for the use of an approved thrombolytic agent to dissociate clusters of circulating metastatic cells, prompting immediate clinical evaluation of a generalized strategy to extend the survival of cancer patients in remission.

MICROENVIRONMENT AND IMMUNOLOGY

- 4483** Suppression of Intratumoral CCL22 by Type I Interferon Inhibits Migration of Regulatory T Cells and Blocks Cancer Progression
David Anz, Moritz Rapp, Stephan Eiber, Viktor H. Koelzer, Raffael Thaler, Sascha Haubner, Max Knott, Sarah Nagel, Michaela Golic, Gabriela M. Wiedemann, Franz Bauernfeind, Cornelia Wurzenberger, Veit Hornung, Christoph Scholz, Doris Mayr, Simon Rothenfusser, Stefan Endres, and Carole Bourquin
Précis: These findings suggest a generalized strategy to block the recruitment of T-regulatory cells to tumors, thereby suppressing immune escape, a finding with important implications for cancer therapy.
- 4494** CD73 Is Associated with Poor Prognosis in High-Grade Serous Ovarian Cancer
Martin Turcotte, Kathleen Spring, Sandra Pommey, Guillaume Chouinard, Isabelle Cousineau, Joshy George, Gregory M. Chen, Deena M.A. Gendoo, Benjamin Haibe-Kains, Thomas Kam, Kurosh Rahimi, Cécile Le Page, Diane Provencher, Anne-Marie Mes-Masson, and John Stagg
Précis: This study highlights clinically relevant roles for a cell surface immunosuppressive enzyme as a prognostic marker and candidate therapeutic target in ovarian cancer.

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4504 Elevated Expression of the C-Type Lectin CD93 in the Glioblastoma Vasculature Regulates Cytoskeletal Rearrangements That Enhance Vessel Function and Reduce Host Survival

Elise Langenkamp, Lei Zhang, Roberta Lugano, Hua Huang, Tamador Elsir Abu Elhassan, Maria Georganaki, Wesam Bazzar, Johan Lööf, George Trendelenburg, Magnus Essand, Fredrik Pontén, Anja Smits, and Anna Dimberg

Précis: The C-type lectin CD93 enhances tumor vascular function by regulating endothelial migration, adhesion, and cytoskeletal rearrangements, and its expression in human glioblastoma vasculature correlates with poor survival outcome.

4517 Tetraspanin CD81 Promotes Tumor Growth and Metastasis by Modulating the Functions of T Regulatory and Myeloid-Derived Suppressor Cells

Felipe Vences-Catalán, Ranjani Rajapaksa, Minu K. Srivastava, Aurelien Marabelle, Chiung-Chi Kuo, Ronald Levy, and Shoshana Levy

Précis: These findings demonstrate that the cell surface tetraspanin CD81, which is widely expressed in cancer, can contribute to immune escape by attenuating the immunosuppressive activity of innate and adaptive cells, which drive malignant progression.

MOLECULAR AND CELLULAR PATHOBIOLOGY

4527 Cytosolic TMEM88 Promotes Invasion and Metastasis in Lung Cancer Cells by Binding DVLS

Xiupeng Zhang, Xinmiao Yu, Guiyang Jiang, Yuan Miao, Liang Wang, Yong Zhang, Yang Liu, Chuifeng Fan, Xuyong Lin, Qianze Dong, Qiang Han, Huanyu Zhao, Yong Han, Xu Han, Xuezhong Rong, Shuting Ding, Endi Wang, and Enhua Wang

Précis: This study reveals the biological roles of TMEM88 with different localization in NSCLC in vivo and in vitro and provides a new potential target for the therapy of lung cancer patients.

4538 The PKC/NF- κ B Signaling Pathway Induces APOBEC3B Expression in Multiple Human Cancers

Brandon Leonard, Jennifer L. McCann, Gabriel J. Starrett, Leah Kosyakovsky, Elizabeth M. Luengas, Amy M. Molan, Michael B. Burns, Rebecca M. McDougale, Peter J. Parker, William L. Brown, and Reuben S. Harris

Précis: By revealing how a DNA mutator factor is upregulated in many human cancers, where it may contribute to pathogenesis and progression, this provocative study suggests new uses for PKC and NF- κ B inhibitors in the neoadjuvant setting to decrease risks of acquired drug resistance and metastasis.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4548 c-Myc Alterations Confer Therapeutic Response and Acquired Resistance to c-Met Inhibitors in MET-Addicted Cancers



Aijun Shen, Lu Wang, Min Huang, Jingya Sun, Yi Chen, Yan-Yan Shen, Xinying Yang, Xin Wang, Jian Ding, and Meiyu Geng

Précis: These findings suggest the idea that alterations to the transcription factor c-Myc confer a generalized mechanism of therapeutic resistance to inhibitors of upstream acting kinases, based on studies of acquired resistance to c-Met kinase inhibitors.

4560 Targeting the MDM2/MDM4 Interaction Interface as a Promising Approach for p53 Reactivation Therapy

Marsha Pellegrino, Francesca Mancini, Rossella Lucà, Alice Coletti, Nicola Giacchè, Isabella Manni, Ivan Arisi, Fulvio Florenzano, Emanuela Teveroni, Marianna Buttarelli, Laura Fici, Rossella Brandi, Tiziana Bruno, Maurizio Fanciulli, Mara D'Onofrio, Giulia Piaggio, Roberto Pellicciari, Alfredo Pontecorvi, Jean Christophe Marine, Antonio Macchiarulo, and Fabiola Moretti

Précis: A novel strategy to reactivate p53 for therapeutic purposes offers increased specificity and potential more limited toxicity, compared to other approaches that have been examined.

4573 Activation Status of the Pregnane X Receptor Influences Vemurafenib Availability in Humanized Mouse Models

A. Kenneth MacLeod, Lesley A. McLaughlin, Colin J. Henderson, and C. Roland Wolf

Précis: These findings show how absorption and metabolism of the melanoma drug vemurafenib influence its systemic availability, elucidating mechanisms potentially underlying therapeutic response, drug resistance, and consequences of multi-drug interactions.

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TUMOR AND STEM CELL BIOLOGY

4582 Cancer Stem Cell Marker Phenotypes Are Reversible and Functionally Homogeneous in a Preclinical Model of Pancreatic Cancer

Joseph S. Dosch, Elizabeth K. Ziemke, Amrith Shettigar, Alnawaz Rehemtulla, and Judith S. Sebolt-Leopold

Précis: These findings suggest that cancer stem cell markers are reversible, with isolated cell subpopulations equally tumorigenic and sensitive to chemotherapy in a mouse model of pancreatic cancer, challenging hierarchically organized models for understanding how cancer stem-like cells contribute to cancer pathogenicity and progression.

4593 Heterochromatin Protein HP1 γ Promotes Colorectal Cancer Progression and Is Regulated by miR-30a



Ming Liu, Feifei Huang, Dan Zhang, Junyi Ju, Xiao-Bin Wu, Ying Wang, Yadong Wang, Yupeng Wu, Min Nie, Zhuchen Li, Chi Ma, Xi Chen, Jin-Yong Zhou, Renxiang Tan, Bo-Lin Yang, Ke Zen, Chen-Yu Zhang, Yu-Gen Chen, and Quan Zhao

Précis: This study identifies a new epigenetic regulatory axis that controls the development of colorectal cancer, with implications for its prognosis and therapy.

4605 Breast Cancer Cells Respond Differentially to Modulation of TGF β 2 Signaling after Exposure to Chemotherapy or Hypoxia

Siobhan K. O'Brien, Liang Chen, Wenyan Zhong, Douglas Armellino, Jiyang Yu, Christine Loreth, Maximillian Follettie, and Marc Damelin

Précis: These findings provide mechanistic insight into how chemotherapy-resistant cell populations emerge and also illustrate the inherent flaws in any treatment strategy that does not address tumor heterogeneity as driven by genetic and epigenetic factors in tumor cells and their tissue microenvironment.

4617 PI3K-mTORC2 but not PI3K-mTORC1 Regulates Transcription of HIF2A/EPAS1 and Vascularization in Neuroblastoma

Sofie Mohlin, Arash Hamidian, Kristoffer von Stedingk, Esther Bridges, Caroline Wigerup, Daniel Bexell, and Sven Pahlman

Précis: This study elucidates expression control mechanisms for HIF-2, a central regulator of cellular responses to hypoxia that is less understood than HIF-1, with practical implications in suggesting how to better target aggressive neuroblastomas, where HIF-2 tends to be selectively overexpressed.

4629 Generation of a Mouse Model of Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System through Combined Deletion of Snf5 and p53

Jessica M.Y. Ng, Daniel Martinez, Eric D. Marsh, Zhe Zhang, Eric Rappaport, Mariarita Santi, and Tom Curran

Précis: These findings offer insight into the development of oligodendrocytes, a connective tissue cell in the central nervous system, and address the lack of preclinical models for a rare pediatric rhabdoid tumor arising from precursors of that cell lineage, known as atypical teratoid/rhabdoid tumors (AT/RT).

4640 A Systematic Analysis Reveals Heterogeneous Changes in the Endocytic Activities of Cancer Cells

Sarah R. Elkin, Nawal Bendris, Carlos R. Reis, Yunyun Zhou, Yang Xie, Kenneth E. Huffman, John D. Minna, and Sandra L. Schmid

Précis: Endocytotic alterations in cancer cells, which affect cell surface expression patterns, have a major influence on cancer phenotypes, highlighting broad-based opportunities to control cancer by modulating endocytic dynamics.

4651 A TDO2-AhR Signaling Axis Facilitates Anoikis Resistance and Metastasis in Triple-Negative Breast Cancer

Nicholas C. D'Amato, Thomas J. Rogers, Michael A. Gordon, Lisa I. Greene, Dawn R. Cochrane, Nicole S. Spoelstra, Travis G. Nemkov, Angelo D'Alessandro, Kirk C. Hansen, and Jennifer K. Richer

Précis: Seminal findings deepen the evidence of a role for tryptophan catabolism in metastasis, intensifying interest in clinical development of small molecule inhibitors of tryptophan catabolic enzymes already at the forefront of the immunotherapy revolution as key mediators of immune escape.

RETRACTION

4665 Retraction: Meeting Report: Inaugural Chemotherapy-Induced Peripheral Neuropathy Symposium, Santa Barbara, CA, February 2015

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ABOUT THE COVER

Lung metastases from an orthotopic syngeneic breast cancer (left, wild type; right, knockout) are shown. The study found that metastases are highly reduced in CD81-deficient mice. Immune suppressor cells, T-regulatory (Treg) cells, and myeloid-derived suppressor cells were impaired in these knockout mice. Wild-type Tregs restored the metastatic phenotype in the knockout animals. For details, see article by Vences-Catalán and colleagues on page 4517.



Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

75 (21)

Cancer Res 2015;75:4439-4665.

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