BREAKING ADVANCES

4593 Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY
COMMENTARIES

4595 Extracellular Matrix Invasion in Metastases and Angiogenesis: Commentary on the Matrigel "Chemoinvasion Assay"
Adriana Albini

4598 The Inaugural Use of Gene Editing for the Study of Tumor Suppressor Pathways in Human Cells—p21WAF1/CIP1
Todd Waldman

REVIEW

4602 Fine-Tuning Cancer Immunotherapy: Optimizing the Gut Microbiome
Jonathan M. Pitt, Marie Véritou, Nadine Waldschmitt, Guido Kroemer, Mathias Chamaillard, Ivo Gomperts Boneca, and Laurence Zitvogel

INTEGRATED SYSTEMS AND TECHNOLOGIES

4608 Myc Expression Drives Aberrant Lipid Metabolism in Lung Cancer
Zoe Hall, Zsusanna Ament, Catherine H. Wilson, Deborah L. Burkhardt, Tom Ashmore, Albert Koulman, Trevor Littlewood, Gerard I. Evan, and Julian L. Griffin
Précis: These results show how MYC drives the production of specific eicosanoids critical for lung cancer cell survival and proliferation, with possible implications for the use of COX and LOX pathway inhibitors for lung cancer therapy.

4619 Molecular Pathology of Patient Tumors, Patient-Derived Xenografts, and Cancer Cell Lines
Sheng Guo, Wubin Qian, Jie Cai, Likan Zhang, Jean-Pierre Wery, and Qi-Xiang Li
Précis: This study describes a new method for cancer diagnosis based on molecular pathology, offering equivalence to histopathology as described for improved accuracy.

MICROENVIRONMENT AND IMMUNOLOGY

4648 Follicular B Lymphomas Generate Regulatory T Cells via the ICOS/ICOSL Pathway and Are Susceptible to Treatment by Anti-ICOS/ICOSL Therapy
Kieu-Suong Le, Marie-Laure Thibult, Sylvain Just-Landi, Sonia Pastor, Françoise Gondois-Rey, Samuel Geanjeaud, Florence Brousais, Reda Bouabdallah, Renaud Colisson, Christophe Caux, Christine Ménétrier-Caux, Dominique Leroux, Lu Xerri, and Daniel Olive
Précis: ICOS+ activated Treg accumulate in follicular lymphoma tissues and inhibit not only conventional T cells but also follicular lymphoma B cells, suggesting that anti-ICOS immunotherapy could be efficacious in this disease setting.

4661 Therapeutic Efficacy of Cancer Stem Cell Vaccines in the Adjuvant Setting
Yangyang Hu, Lin Lu, Yang Xia, Xin Chen, Alfred E. Chang, Robert E. Hollingsworth, Elaine Hurt, John Owen, Jeffrey S. Moyer, Mark E.P. Prince, Fu Dai, Yangyi Bao, Yi Wang, Joel Whitfield, Jian-Chuan Xia, Shiang Huang, Max S. Wicha, and Qiao Li
Précis: These findings offer a preclinical proof of concept for a more effective use of cancer stem-like cell-targeting dendritic cell vaccines in the adjuvant setting, that is, after excision of a primary tumor whose presence enforces immunosuppression.
Checkpoint Antibodies but not T Cell–Recruiting Diabodies Effectively Synergize with TIL-Inducing γ-Irradiation
Michael Hettich, Jayashree Lahoti, Shruthi Prasad, and Gabriele Niedermann
Précis: These findings suggest caution in the use of T cell–recruiting bispecific antibodies for the treatment of solid tumors, but they also reveal that immune checkpoint-blocking antibodies can synergize powerfully with radiation to cure even very large tumors.

Eritoran Suppresses Colon Cancer by Altering a Functional Balance in Toll-like Receptors That Bind Lipopolysaccharide
Wei-Ting Kuo, Tsung-Chun Lee, and Linda Chia-Hui Yu
Précis: These findings offer a preclinical proof of concept for use of the experimental sepsis drug eritoran as a cancer therapeutic to manipulate host-microbial interactions and to improve the management of colorectal cancer.

Oncoprotein HBXIP Modulates Abnormal Lipid Metabolism and Growth of Breast Cancer Cells by Activating the LXR/SREBP-1c/FAS Signaling Cascade
Yu Zhao, Hang Li, Yingyi Zhang, Leilei Li, Runping Fang, Yinghui Li, Qian Liu, Weiying Zhang, Liyan Qiu, Fabao Liu, Xiaodong Zhang, and Lihong Ye
Précis: These findings elucidate how aberrant lipid metabolism pathways sustain breast cancer cell growth, deepening the evidence that targeting these pathways may be therapeutically useful.

PI3Kα Is a Negative Regulator of Growth and the Warburg Effect in Glioblastoma
Sameer Agnihotri, Brian Golbourn, Xi Huang, Marc Remke, Susan Younger, Rob A. Cairns, Alan Chalil, Christian A. Smith, Stacey-Lynn Krumholtz, Danielle Mackenzie, Patricia Rakopoulos, Vijay Ramaswamy, Michael S. Rakopoulos, Paul S. Mischel, Gregory N. Fuller, Cynthia Hawkins, William L. Stanford, Michael D. Taylor, Gelareh Zadeh, and James T. Rutka
Précis: These findings offer a mechanistic rationale to attack aggressive brain cancers by reprogramming a critical metabolic pathway that sustains them.

CSN1 Somatic Mutations in Penile Squamous Cell Carcinoma
Andrew Feber, Daniel C. Worth, Ankur Chakravarthy, Patricia de Winter, Kunal Shah, Manit Anya, Muhammad Saqib, Raj Nigam, Peter R. Malone, Wei Shen Tan, Simon Rodney, Alex Freeman, Charles Jameson, Gareth A. Wilson, Tom Powles, Stephan Beck, Tim Fenton, Tyson V. Sharp, Asif Muneer, and John D. Kelly
Précis: This whole exome sequencing study of penile cancer, which is rare in developed countries but a significant burden in developing countries, offers the first comprehensive analysis of somatic genetic alterations in this malignancy.

miR-196b Is Epigenetically Silenced during the Premalignant Stage of Lung Carcinogenesis
Carmen S. Tellez, Daniel E. Juri, Kieu Do, Maria A. Picchi, Teresa Wang, Gang Liu, Avrum Spira, and Steven A. Belinsky
Précis: Targeted delivery of miR-196b, a tumor suppressor microRNA, may have preventive or therapeutic utility for the management of lung cancer.

Rictor/mTORC2 Drives Progression and Therapeutic Resistance of HER2-Amplified Breast Cancers
Meghan Morrison Joly, Donna J. Hicks, Bayley Jones, Violeta Sanchez, Monica Valeria Estrada, Christian Young, Michelle Williams, Brent N. Rexer, Dos D. Sarbassov, William J. Muller, Dana Bramley-Sieders, and Rebecca S. Cook
Précis: mTORC2 inhibition may offer a promising therapeutic strategy to help eradicate HER2-amplified breast cancers, especially in those cases where Akt signaling is activated or tumors are resistant HER2 targeted therapy.
Multiregion Whole-Exome Sequencing Uncovers the Genetic Evolution and Mutational Heterogeneity of Early-Stage Metastatic Melanoma

Katja Harbst, Martin Lauss, Helena Cirenajwis, Karolin Isaksson, Frida Rosengren, Therese Torngren, Anders Kvist, Maria C. Johansson, Johan Vallon-Christersson, Bo Baldetorp, Åke Borg, Håkan Olsson, Christian Ingvar, Ana Carneiro, and Göran Jonsson

Précis: A multiregion sequencing approach reveals the diverse genetic events underlying intratumoral heterogeneity over the course of early metastatic melanoma, with possible implications for exploiting the mutational spectrum across multiple tumor specimens as a more reliable prognostic indicator.

Low-Dose Paclitaxel Reduces S100A4 Nuclear Import to Inhibit Invasion and Hematogenous Metastasis of Cholangiocarcinoma

Massimiliano Cadamuro, Gaia Spagnuolo, Luisa Sambado, Stefano Indraccolo, Giorgia Nardo, Antonio Rosato, Simone Brivio, Chiara Caslini, Tommaso Stecca, Marco Massani, Niccolò Bassi, Eugenio Novelli, Carlo Spirlì, Luca Fabris, and Mario Strazzabosco

Précis: Low-dose chemotherapy may be more useful than traditional doses to block the metastatic progression of certain poorly managed tumors such as cholangiocarcinoma, an aggressive and poorly managed cancer of the liver bile duct.

Cholesterol Metabolism and Prostate Cancer Lethality


Précis: High intratumoral expression of squalene monoxygenase, the second rate-limiting enzyme of cholesterol synthesis, is found to be associated with a high risk of lethality in prostate cancer patients.

Inhibiting DX2-p14/ARF Interaction Exerts Antitumor Effects in Lung Cancer and Delays Tumor Progression

Ah-Young Oh, Youn Sang Jung, Jiseon Kim, Jee-Hyun Lee, Jung Hyun Cho, Ho-Young Chun, Soyoung Park, Hyunchul Park, Sikeun Lim, Nam-Chul Ha, Jong Sook Park, Choon-Sik Park, Gyu-Yong Song, and Bum-Joon Park

Précis: These results suggest a new strategy to attenuate lung cancer progression by targeting the interaction of a new suppressor of p14/ARF function with potentially special relevance to treat cancers, which arise in heavy smokers.

Novel Anticancer Agents Based on Targeting the Trimer Interface of the PRL Phosphatase

Yunpeng Bai, Zhi-Hong Yu, Sijiu Liu, Ruo-Yu Zhang, Li-Fan Zeng, Sheng Zhang, and Zhong-Yin Zhang

Précis: These results offer a preclinical proof of concept for the use of small molecules that block trimerization of PRL phosphatases, a little explored class of important cancer target molecules.

mTORC1-Driven Tumor Cells Are Highly Sensitive to Therapeutic Targeting by Antagonists of Oxidative Stress

Jing Li, Sejeong Shin, Yang Sun, Sang-Oh Yoon, Chenggang Li, Erik Zhang, Jane Yu, Jianming Zhang, and John Blenis

Précis: These findings offer preclinical proof of concept for a combination strategy to selectively increase the cytotoxicity of mTORC1 inhibitors, which have performed poorly in clinic, based on cotargeting glutathione-controlled oxidative stress pathways.

Metastasis Stimulation by Hypoxia and Acidosis-Induced Extracellular Lipid Uptake Is Mediated by Proteoglycan-Dependent Endocytosis


Précis: This study unravels mechanisms of cancer cell adaptation to major stress factors of the tumor microenvironment associated with increased aggressiveness.
4841  Pexmetinib: A Novel Dual Inhibitor of Tie2 and p38 MAPK with Efficacy in Preclinical Models of Myelodysplastic Syndromes and Acute Myeloid Leukemia
Précis: These results provide preclinical proof of concept for an experimental drug that targets the key pathogenic contributions of angiopoietin-1 to the development of malignant stem-like myeloid cells.

4850  Diverse, Biologically Relevant, and Targetable Gene Rearrangements in Triple-Negative Breast Cancer and Other Malignancies
Timothy M. Shaver, Brian D. Lehmann, J. Scott Beeler, Chung-Ji Liu, Zhu Li, Hailing Jin, Thomas P. Stricker, Yu Shyr, and Jennifer A. Pietenpol
Précis: This study highlights the importance of considering noncoding gene rearrangement fusions in cancer, along with the need to advance gene fusion detection technologies for characterizing the molecular features of heterogeneous cancers in this regard.

4861  Reduced Expression of Histone Methyltransferases KMT2C and KMT2D Correlates with Improved Outcome in Pancreatic Ductal Adenocarcinoma
Précis: These results highlight the importance of epigenetic modulation in pancreatic cancer, based on impact on patient survival, with possible implications for therapeutic management.

4872  MicroRNA-211 Enhances the Oncogenicity of Carcinogen-Induced Oral Carcinoma by Repressing TCF12 and Increasing Antioxidant Activity
Yi-Fen Chen, Cheng-Chieh Yang, Shou-Yen Kao, Chung-Ji Liu, Shu-Chun Lin, and Kuo-Wei Chang
Précis: These findings provide new insight into the molecular pathways that promote the development of oral cancers in response to carcinogenic agents.

4887  (Z)-3,5,4’-Trimethoxystilbene Limits Hepatitis C and Cancer Pathophysiology by Blocking Microtubule Dynamics and Cell-Cycle Progression
Précis: Z-TMS is a potent antiviral and anticancer drug that appears to protect the liver from damage yet overcome drug resistance.

LETTERS TO THE EDITOR

4908  Urokinase Exerts Antimetastatic Effects by Dissociating Clusters of Circulating Tumor Cells—Letter
Juan Garona and Daniel F. Alonso

4909  Urokinase Antimetastatic Effects—Letter
Shahzad M. Minshahi, Eric Pujade-Lauraine, Claudine Soria†, Marc Pocard, Massoud Mirshahi, and Jeannette Soria

4910  Antimetastatic Effect by Targeting CTC Cluster—Response
Jin Woo Choi, Kwon-Ha Yoon, and Seok Hyun Yun
ABOUT THE COVER

Current cancer taxonomy is based on the organ and tissue origin of tumors (histopathology), which can potentially be reflected by gene expression as well. This makes it possible to establish equivalency between histopathology and molecular pathology by transcriptome expression. Guo and colleagues report seven distinct gene expression profiles corresponding to seven major cancer types with high within-type and generally low between-type correlation. The described algorithm can be a foundation for the development of future cancer diagnostics. Color bars at the top and to the left denote cancer types. For details, see article by Guo and colleagues on page 4619.

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