

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—p21^{WAF1/CIP1}
Todd Waldman

REVIEW

- 4602** Fine-Tuning Cancer Immunotherapy: Optimizing the Gut Microbiome
Jonathan M. Pitt, Marie Vétizou, 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, Zsuzsanna 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, Likun 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.

- 4627** Design and Reporting of Targeted Anticancer Preclinical Studies: A Meta-Analysis of Animal Studies Investigating Sorafenib Antitumor Efficacy
James Mattina, Nathalie MacKinnon, Valerie C. Henderson, Dean Fergusson, and Jonathan Kimmelman

Précis: Poor adherence to preclinical design and reporting guidelines, coupled with publication bias, threatens the reproducibility of preclinical research of candidate therapeutics, potentially overestimating their clinical utility.

- 4637** Remodeling of the Epithelial–Connective Tissue Interface in Oral Epithelial Dysplasia as Visualized by Noninvasive 3D Imaging
Rahul Pal, Tuya Shilagard, Jinping Yang, Paula Villarreal, Tyra Brown, Suimin Qiu, Susan McCammon, Vicente Resto, and Gracie Vargas

Précis: Novel microscopic methods reveal topographical deformations in oral epithelial atypia that can distinguish precursor lesions from normal/benign mucosa.

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 Granjeaud, Florence Broussais, Reda Bouabdallah, Renaud Colisson, Christophe Caux, Christine Ménétrier-Caux, Dominique Leroux, Luc 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.

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- 4673** 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 cautions in the use of T cell–recruiting bispecific antibodies for the treatment of solid tumors, but also reveal that immune checkpoint-blocking antibodies can synergize powerfully with radiation to cure even very large tumors.

- 4684** 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.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 4696** Oncoprotein HBXIP Modulates Abnormal Lipid Metabolism and Growth of Breast Cancer Cells by Activating the LXRs/SREBP-1c/FAS Signaling Cascade

Yu Zhao, Hang Li, Yingyi Zhang, Leilei Li, Rungping Fang, Yinghui Li, Qian Liu, Weiyang 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.

- 4708** PINK1 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. Taccone, 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.

- 4720** CSN1 Somatic Mutations in Penile Squamous Cell Carcinoma



Andrew Feber, Daniel C. Worth, Ankur Chakravarthy, Patricia de Winter, Kunal Shah, Manit Arya, 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.

- 4728** Tumor Suppressor HIPK2 Regulates Malignant Growth via Phosphorylation of Notch1

Eun-Jung Ann, Mi-Yeon Kim, Ji-Hye Yoon, Ji-Seon Ahn, Eun-Hye Jo, Hye-Jin Lee, Hyun-Woo Lee, Hyeok-Gu Kang, Dong Wook Choi, Kyung-Hee Chun, Ji Shin Lee, Cheol Yong Choi, Adolfo A. Ferrando, Keesook Lee, and Hee-Sae Park

Précis: In revealing an important mechanism of Notch1 stability, the results of this study could offer a therapeutic strategy to block Notch1-dependent progression in many types of cancer.

- 4741** 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.

- 4752** 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 Brantley-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.



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4765 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 Törngren, Anders Kvist, Maria C. Johansson, Johan Vallon-Christersson, Bo Baldetorp, Åke Borg, Håkan Olsson, Christian Ingvar, Ana Carneiro, and Göran Jönsson

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.

4775 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, Nicolò Bassi, Eugenio Novelli, Carlo Spirli, 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.

PREVENTION AND EPIDEMIOLOGY

4785 Cholesterol Metabolism and Prostate Cancer Lethality

Konrad H. Stopsack, Travis A. Gerke, Jennifer A. Sinnott, Kathryn L. Penney, Svitlana Tyekucheva, Howard D. Sesso, Swen-Olof Andersson, Ove Andrén, James R. Cerhan, Edward L. Giovannucci, Lorelei A. Mucci, and Jennifer R. Rider

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

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

4791 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, Soyoun Park, Hyun-chul 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.

4805 Novel Anticancer Agents Based on Targeting the Trimer Interface of the PRL Phosphatase

Yunpeng Bai, Zhi-Hong Yu, Sijiu Liu, Lujuan Zhang, 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.

4816 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.

4828 Metastasis Stimulation by Hypoxia and Acidosis-Induced Extracellular Lipid Uptake Is Mediated by Proteoglycan-Dependent Endocytosis



Julien A. Menard, Helena C. Christianson, Paulina Kucharzewska, Erika Bourseau-Guilmain, Katrin J. Svensson, Eva Lindqvist, Vineesh Indira Chandran, Lena Kjellén, Charlotte Welinder, Johan Bengzon, Maria C. Johansson, and Mattias Belting

Précis: This study unravels mechanisms of cancer cell adaptation to major stress factors of the tumor microenvironment associated with increased aggressiveness.

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4841 **Pexmetinib: A Novel Dual Inhibitor of Tie2 and p38 MAPK with Efficacy in Preclinical Models of Myelodysplastic Syndromes and Acute Myeloid Leukemia**

Lohith Bachegowda, Kerry Morrone, Shannon L. Winski, Ioannis Mantzaris, Matthias Bartenstein, Nandini Ramachandra, Orsi Giricz, Vineeth Sukrithan, George Nwankwo, Samira Shahnaz, Tushar D. Bhagat, Sanchari Bhattacharyya, Amer Assal, Aditi Shastri, Shanisha Gordon-Mitchell, Andrea Pellagatti, Jacqueline Boulwood, Carolina Schinke, Yiting Yu, Chandan Guha, James Rizzi, Jennifer Garrus, Suzy Brown, Lance Wollenberg, Grant Hogeland, Dale Wright, Mark Munson, Mareli Rodriguez, Stefan Gross, David Chantry, Yiyu Zou, Leonidas C. Plataniias, Laurence E. Burgess, Kith Pradhan, Ulrich Steidl, and Amit Verma

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-I Li, Zhu Li, Hailing Jin, Thomas P. Stricker, Yu Shyr, and Jennifer A. Pietsenpol

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**

Joshua B.N. Dawkins, Jun Wang, Eleni Maniati, James A. Heward, Lola Koniali, Hemant M. Kocher, Sarah A. Martin, Claude Chelala, Frances R. Balkwill, Jude Fitzgibbon, and Richard P. Grose

Précis: These results highlight the importance of epigenetic modulation in pancreatic cancer, based on impact on patient survival, with possible implications for therapeutic management.

TUMOR AND STEM CELL BIOLOGY

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**

Charles B. Nguyen, Hari Kotturi, Gulam Waris, Altaf Mohammed, Parthasarathy Chandrakesan, Randal May, Sripathi Sureban, Nathaniel Weygant, Dongfeng Qu, Chinthalapally V. Rao, Danny N. Dhanasekaran, Michael S. Bronze, Courtney W. Houchen, and Naushad Ali

Précis: Z-TMS is a potent antiviral and anticancer drug that appears to protect the liver from damage yet overcome drug resistance.

4897 **The Ubiquitin-like Protein FAT10 Stabilizes eEF1A1 Expression to Promote Tumor Proliferation in a Complex Manner**

Xiuxia Liu, Leifeng Chen, Jin Ge, Chen Yan, Zixi Huang, Junwen Hu, Chongyu Wen, Ming Li, Da Huang, Yumin Qiu, Haibin Hao, Rongfa Yuan, Jun Lei, Xin Yu, and Jianghua Shao

Précis: This work shows how a modifier of protein ubiquitylation stabilizes its substrates, advancing understanding of its biological function and its role in cancer.

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**

ShahSultan Mirshahi, 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

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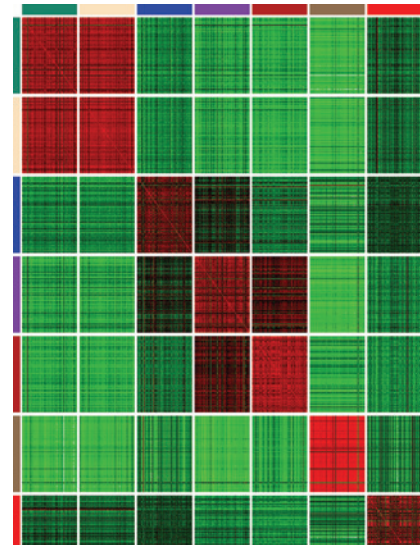
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ABOUT THE COVER

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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