

BREAKING ADVANCES

- 763** Highlights from Recent Cancer Literature

CANCER RESEARCH 75th ANNIVERSARY COMMENTARIES

- 765** Tobacco Causes Human Cancers—A Concept Founded on Epidemiology and an Insightful Experiment Now Requires Translation Worldwide
Lawrence A. Loeb
- 767** A Retrospective: On Clinical Studies with 5-Fluorouracil
V. Craig Jordan

REVIEW

- 769** Oxygen-Enhanced MRI Is a Major Advance in Tumor Hypoxia Imaging
Mark W. Dewhirst and Samuel R. Brier

INTEGRATED SYSTEMS AND TECHNOLOGIES

- 773** Comprehensive *Ex Vivo* Transposon Mutagenesis Identifies Genes That Promote Growth Factor Independence and Leukemogenesis
Yabin Guo, Barrett L. Updegraff, Sunho Park, Deniz Durakoglugil, Victoria H. Cruz, Sarah Maddux, Tae Hyun Hwang, and Kathryn A. O'Donnell
Précis: This study presents a broadly applicable approach for identifying and classifying functionally relevant genes in hematopoietic malignancies and offers new insights into the drivers of leukemogenesis.
- 787** Oxygen-Enhanced MRI Accurately Identifies, Quantifies, and Maps Tumor Hypoxia in Preclinical Cancer Models
James P.B. O'Connor, Jessica K.R. Boulton, Yann Jamin, Muhammad Babur, Katherine G. Finegan, Kaye J. Williams, Ross A. Little, Alan Jackson, Geoff J.M. Parker, Andrew R. Reynolds, John C. Waterton, and Simon P. Robinson
Précis: These findings validate a novel MRI method for imaging tumor hypoxia that fulfills an unmet clinical need and can be readily translated into clinical studies.

- 796** Accumulated Metabolites of Hydroxybutyric Acid Serve as Diagnostic and Prognostic Biomarkers of Ovarian High-Grade Serous Carcinomas
Mika Hilvo, Ines de Santiago, Peddinti Gopalacharyulu, Wolfgang D. Schmitt, Jan Budczies, Marc Kuhberg, Manfred Dietel, Tero Aittokallio, Florian Markowitz, Carsten Denkert, Jalid Sehouli, Christian Frezza, Silvia Darb-Esfahani, and Elena Ioana Braicu
Précis: This study reveals a distinct metabolic signature in patients with a highly malignant form of ovarian cancer that offers much needed new biomarkers for monitoring disease progression and patient outcome.

MICROENVIRONMENT AND IMMUNOLOGY

- 805** Macrophage Infiltration and Alternative Activation during Wound Healing Promote MEK1-Induced Skin Carcinogenesis
Christine Weber, Stephanie B. Telerman, Andreas S. Reimer, Ines Sequeira, Kifayathullah Liakath-Ali, Esther N. Arwert, and Fiona M. Watt
Précis: These findings shed new light on the role of macrophages during the early stages of tumor formation, demonstrating that their accumulation during wound healing and their gross consumption of arginine is a foreboding sign of tumor development.
- 818** Hypoxia-Induced Epithelial-to-Mesenchymal Transition in Hepatocellular Carcinoma Induces an Immunosuppressive Tumor Microenvironment to Promote Metastasis
Long-Yun Ye, Wei Chen, Xue-Li Bai, Xing-Yuan Xu, Qi Zhang, Xue-Feng Xia, Xu Sun, Guo-Gang Li, Qi-Da Hu, Qi-Han Fu, and Ting-Bo Liang
Précis: These findings illuminate a signaling network that integrates hypoxic and innate immune responses in the tumor microenvironment, coordinating the creation of an immunosuppressive, prometastatic state that drives liver cancer progression.

MOLECULAR AND CELLULAR PATHOBIOLOGY

- 831** JARID1D Is a Suppressor and Prognostic Marker of Prostate Cancer Invasion and Metastasis
Na Li, Shilpa S. Dhar, Tsai-Yu Chen, Pu-Yeh Kan, Yongkun Wei, Jae-Hwan Kim, Chia-Hsin Chan, Hui-Kuan Lin, Mien-Chie Hung, and Min Gyu Lee
Précis: This study provides mechanistic insights into the tumor suppressive role of the Y chromosome, in which epigenetic modification by a histone demethylase attenuates prostate cancer cell invasion, with potential implications for prognosis and treatment of metastatic disease.

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844 Mesenchymal Tumorigenesis Driven by TSC2 Haploinsufficiency Requires HMGA2 and Is Independent of mTOR Pathway Activation

Jeanine D'Armiento, Takayuki Shiomi, Sarah Marks, Patrick Geraghty, Devipriya Sankarasharma, and Kiran Chada

Précis: These findings identify a common transcriptional pathway controlled by the TSC tumor suppressor gene family, where inactivations can drive the formation of a variety of mesenchymal tumors.

855 NADPH Oxidase 1 Activity and ROS Generation Are Regulated by Grb2/Cbl-Mediated Proteasomal Degradation of NoxO1 in Colon Cancer Cells

Jung Hee Joo, Hyunjin Oh, Myungjin Kim, Eun Jung An, Rae-Kwon Kim, So-Young Lee, Dong Hoon Kang, Sang Won Kang, Cheol Keun Park, Hoguen Kim, Su-Jae Lee, Daekee Lee, Jae Hong Seol, and Yun Soo Bae

Précis: These findings provide new mechanistic insights into the regulation of ROS production in colon cancer cells and offer new opportunities to investigate the therapeutic modulation of intracellular ROS levels in tumor cells.

866 IL6 Trans-signaling Promotes KRAS-Driven Lung Carcinogenesis

Gavin D. Brooks, Louise McLeod, Sultan Alhayyani, Alistair Miller, Prudence A. Russell, Walter Ferlin, Stefan Rose-John, Saleela Ruwanpura, and Brendan J. Jenkins

Précis: This study provides mechanistic insight into the cytokine signaling pathways that potentiate KRAS-driven lung adenocarcinoma, highlighting IL6 trans-signaling as a potential therapeutic targeting strategy.

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

877 Penfluridol: An Antipsychotic Agent Suppresses Metastatic Tumor Growth in Triple-Negative Breast Cancer by Inhibiting Integrin Signaling Axis

Alok Ranjan, Parul Gupta, and Sanjay K. Srivastava

Précis: These findings highlight a clinically approved antipsychotic drug with the potential to be repositioned immediately to treat metastatic triple-negative breast cancer in clinical trials.

891 A Small-Molecule Antagonist of the β -Catenin/TCF4 Interaction Blocks the Self-Renewal of Cancer Stem Cells and Suppresses Tumorigenesis

Liang Fang, Qionghua Zhu, Martin Neuenschwander, Edgar Specker, Annika Wulf-Goldenberg, William I. Weis, Jens P. von Kries, and Walter Birchmeier

Précis: A newly identified small-molecule inhibitor of canonical Wnt signaling exerts potent antitumor activity and prompts further preclinical characterization in autochthonous models of Wnt-driven malignancies, such as colorectal cancer.

902 Effects of Anticancer Drugs on Chromosome Instability and New Clinical Implications for Tumor-Suppressing Therapies



Hee-Sheung Lee, Nicholas C.O. Lee, Natalay Kouprina, Jung-Hyun Kim, Alex Kagansky, Susan Bates, Jane B. Trepel, Yves Pommier, Dan Sackett, and Vladimir Larionov

Précis: This report defines increased chromosomal instability (CIN) as a newly identified outcome of many currently used anticancer drugs, with implications for the development of new therapeutic strategies that target and leverage the CIN phenotype in cancer cells.

912 Multinucleation and Mesenchymal-to-Epithelial Transition Alleviate Resistance to Combined Cabazitaxel and Antiandrogen Therapy in Advanced Prostate Cancer

Sarah K. Martin, Hong Pu, Justin C. Penticuff, Zheng Cao, Craig Horbinski, and Natasha Kyprianou

Précis: Efficacious antitumor responses triggered by abazitaxel second-line chemotherapy for metastatic prostate cancer administered in combination with antiandrogens rely greatly on the status and responsiveness of the androgen receptor, with potential implications for patient stratification.

927 miR-34a Silences c-SRC to Attenuate Tumor Growth in Triple-Negative Breast Cancer

Brian D. Adams, Vikram B. Wali, Christopher J. Cheng, Sachi Inukai, Carmen J. Booth, Seema Agarwal, David L. Rimm, Balázs Györfy, Libero Santarpia, Lajos Pusztai, W. Mark Saltzman, and Frank J. Slack

Précis: These findings provide preclinical evidence that miR-34a suppresses triple-negative breast cancer, supporting investigation to develop it as a targeted therapeutic strategy currently lacking in this disease.

TUMOR AND STEM CELL BIOLOGY

940 Injury-Driven Stiffening of the Dermis Expedites Skin Carcinoma Progression

Venugopal R. Mittapalli, Josef Madl, Stefanie Löffek, Dimitra Kiritsi, Johannes S. Kern, Winfried Römer, Alexander Nyström, and Leena Bruckner-Tuderman

Précis: This study shows how a genetic skin disorder rapidly progresses to an aggressive skin cancer, identifying promising therapeutic targets within the compromised dermal microenvironment that may limit carcinogenesis.

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952 SSBP1 Suppresses TGF β -Driven Epithelial-to-Mesenchymal Transition and Metastasis in Triple-Negative Breast Cancer by Regulating Mitochondrial Retrograde Signaling



Hong-Lin Jiang, He-Fen Sun, Shui-Ping Gao, Liang-Dong Li, Sheng Huang, Xin Hu, Sheng Liu, Jiong Wu, Zhi-Ming Shao, and Wei Jin

Précis: These findings define an aberrant signaling process in mitochondria and show how it contributes to driving metastasis in triple-negative breast cancer, a particularly aggressive type of this disease.

965 Targeting the WASF3–CYFIP1 Complex Using Stapled Peptides Suppresses Cancer Cell Invasion

Yong Teng, Abdulaziz Bahassan, Dayong Dong, Laura E. Hanold, Xiaou Ren, Eileen J. Kennedy, and John K. Cowell

Précis: Targeting a protein-protein interaction central to the metastatic process highlights a peptide-based approach that might help eradicate advanced cancer.

974 Oncogenic Fusion Gene *CD74-NRG1* Confers Cancer Stem Cell–like Properties in Lung Cancer through a IGF2 Autocrine/Paracrine Circuit



Takahiko Murayama, Takashi Nakaoku, Masato Enari, Tatsunori Nishimura, Kana Tominaga, Asuka Nakata, Arinobu Tojo, Sumio Sugano, Takashi Kohno, and Noriko Gotoh

Précis: A recently identified oncogenic fusion gene in lung adenocarcinoma is shown to drive and maintain cancer stem cell-like phenotypes, with implications for targeting the fusion gene product to eradicate drug-refractory tumor cells.

CORRECTION

984 Correction: Tumor Angiogenesis Mediated by Myeloid Cells Is Negatively Regulated by CEACAM1

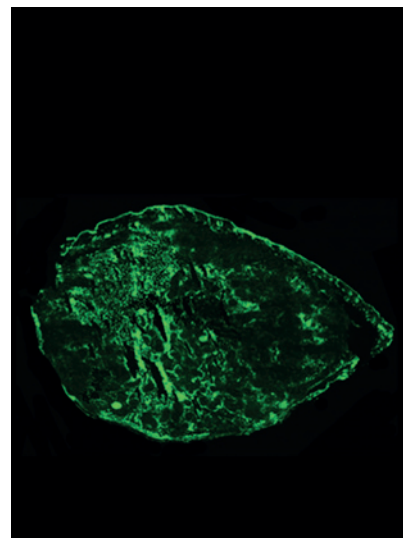


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ABOUT THE COVER

The longitudinal relaxation rate of protons is increased when subjects switch from breathing air to inhaling 100% oxygen. This effect when detected by MRI scanning is termed oxygen-enhanced MRI. It was found that this technique—in combination with measurements of perfusion—was capable of *in vivo* mapping of tumor hypoxia, distinguishing tumor subregions with low oxygen tension from well-oxygenated tumor tissue. Pimonidazole adduct formation immunofluorescence was used to validate these findings. Oxygen-enhanced MRI can be performed readily on conventional clinical scanners, so the technique has potential for rapid clinical translation. For details, see article by O'Connor and colleagues on page 787.



Cancer Research

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